A Dissertation on

A CLINICAL STUDY OF RETINOBLASTOMA AND ITS MANAGEMENT

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI

With partial fulfillment of the regulations for the award

of the degree of

M.S.(OPHTHALMOLOGY)

BRANCH- lll

MADRAS MEDICAL COLLEGE AND RESEARCH INSTITUTE

CHENNAI-600 003

APRIL 2012

CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY OF RETINOBLASTOMA AND ITS MANAGEMENT"** is a bonafide record of the research work done by **Dr. SANGEETHA RAJAMONY** Post graduate in Regional Institute of Ophthalmology, Madras Medical College and Research Institute, Government General Hospital,Chennai-03, in partial fulfillment of the regulations laid down by The Tamil Nadu Dr.M.G.R. Medical University for the award of M.S. Ophthalmology Branch III, under my guidance and supervision during the academic years 2009-2012.

Dr.M.SUBHASHINI,M.S.,D.O.,
Chief Department of Orbit and Oculoplasty
Regional Institute of Ophthalmology
Govt Ophthalmic Hospital
Chennai-600 008

Dr.K.VASANTHA,M.S.,FRCS.,
Director and Professor,
Regional Institute of Ophthalmology
Govt Ophthalmic Hospital
Chennai-600 008

Dr.V.KANAGASABAI,M.D.,Ph.D.,

Dean,
Madras Medical College &
Govt. General Hospital,
Chennai-600 003

ACKNOWLEDGEMENT

I express my sincere thanks to **Prof.Dr.V.Kanagasabai,** M.D.,Ph.D., Dean Madras Medical College for permitting me to conduct this study.

I am grateful to **Prof.Dr.K.Vasantha**, M.S., F.R.C.S., Director and Superintendent, RIO GOH, Chennai, for having assigned me this interesting topic and guiding me.

I express my gratitude to **Prof.Dr.M.Subhashini**, M.S., D.O., Chief Department of Orbit and Oculoplasty who with her vast knowledge and experience provided me with all the necessary facilities and guidance.

I am thankful to **Prof.Dr.Jayasuganthi** M.S.,D.O., Chief Retina services and **Prof.Dr.Zaibunniza** for their valuable guidance. I wish to express my sincere thanks to **Prof.Dr.Rajavelu Indira**,M.D., Professor of Pathology for rendering her valuable support and guidance.

I am grateful to Assistant Professors **Dr.Yogeswari.A** and **Dr.A.Samarapuri** for helping me in the study. I am also thankful to Assisstant Professors **Dr.K.Rajasekar** and **Dr.A.Palaniraj**.

I express my gratitude to all the Professors, Assistant professors and all my colleagues who helped me in bringing out this study

Finally I am indebted to all my patients and their family for their sincere co-operation for completion of this study

INDEX

PART 1

INTRODUCTION

Retinoblastoma is the most common primary intraocular malignancy of childhood [1]. On a global scale, there are 11 cases per million children, 5 years and younger with this tumour. In India, there are 0.6 cases per 1, 00,000 children. 9-10 % of all Pediatric cancer patients (<14 years) in India have retinoblastoma [2].

Retinoblastoma was first described in 1597, and prognosis was dismal through the nineteenth century, at which time enucleation became more widely accepted [3]. In the 20th century, survival has dramatically increased from around 5 percent to over 95 percent in the developed countries, making retinoblastoma one of the success stories in childhood cancer [4].

When retinoblastoma remains confined to the eye, it has one of the best survival rates of all the childhood cancers, but once the spread occurs outside the globe, the treatment needs to be more aggressive and many children do not survive. Management of the child with metastatic disease remains a considerable challenge to all concerned [5]. An early diagnosis is, therefore, of paramount importance in the survival of the child.

HISTORICAL BACKGROUND

Peter Pawius of Amsterdam provided the first description of a tumor resembling retinoblastoma in 1597. The tumor was described as filled with a "substance similar to brain tissue mixed with thick blood and like crushed stone” [6].

In 1805, William Hey coined the term fungus haematodes, which he used to describe as a fungating mass affecting the globe of the eye and destroying its internal organization [7]. In 1809, Wardrop gave the first accurate description of retinoblastoma and concluded that the tumor arose from the retina. He advocated early enucleation [8]. In 1864, Virchow named the tumor a glioma of the retina, supporting glial cells as the cell of origin of the tumor [9].

Flexner (1891) and Wintersteiner (1897) described the histology of retinoblastoma. The rosettes were named after them [10]. The term retinoblastoma was coined by Verhoeff (1922) [11]. Von Graffe (1884) advocated enucleation of eye with long optic stump. Hilgartner (1903) first used external beam radiotherapy and Kupfer (1953) used chemotherapy for retinoblastoma. Reese- Ellsworth (1958) proposed a classification of retinoblastoma [12].

EPIDEMIOLOGY

Retinoblastoma is the most frequent neoplasm of the eye in childhood and accounts for 3% of all pediatric cancers [13]. Worldwide the incidence of retinoblastoma is 1 in 14,000 to 18,000 live births, depending upon the country. 250-300 new cases are diagnosed yearly in western countries [14]. Retinoblastoma occurs primarily in children less than 5 years, with a median age of diagnosis of 24 months in children with unilateral disease and 9-12 months in children with bilateral disease [15]. There is no racial of gender predilection for retinoblastoma. In 60% of cases, the disease is unilateral; of these cases 15% are hereditary. Retinoblastoma is bilateral in about 40% of cases. All bilateral and multifocal unilateral forms are hereditary [16].

The incidence rates are similar in North America, Europe and Australia, higher in Central and South America and even higher in Asia and Africa. This pattern supports the hypothesis of higher retinoblastoma incidence in less industrialized countries. The varied incidence is due to difference in occurrence of unilateral non-heritable disease. The incidence of heritable form is relatively constant. Providing strong evidence that environmental influences play little role in the etiology of the hereditary forms of this tumour [17].

PATHOGENESIS

Retinoblastoma arises from the malignant transformation of primitive retinal cells due to mutation in the Rb gene in chromosome 13q14 [18].

Knudson's two hit hypothesis:

In 1971, Knudson proposed that a developing retinoblast must acquire mutations in both cellular copies of the *Rb* gene for retinoblastoma to develop. This concept also established that "recessive" cancer genes, or the loss of tumor suppressor genes, can predispose to cancer by autosomal-dominant inheritance, although they function in a recessive manner at the cellular level [19].

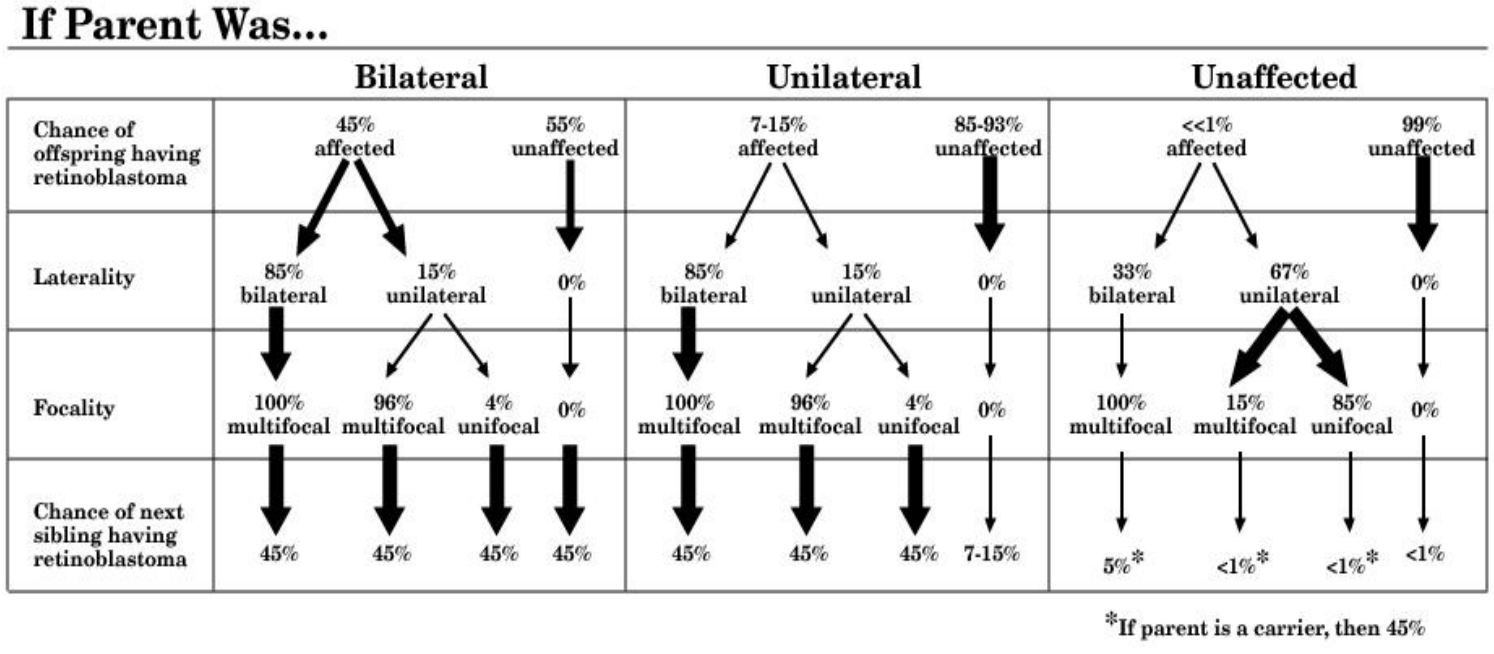
Genetic forms of retinoblastoma:

1. **Somatic/Non-heritable:** The most common presentation of retinoblastoma is the unilaterally affected child with no family history. These children usually have no germline mutation in the *Rb* gene, they do not develop tumors in the second eye, they are not predisposed to second primary cancers, and they do not transmit the disease to their children [20]. Nonheritable retinoblastoma accounts for about 60 percent of cases and is due to two separate somatic mutations of both cellular copies of the *Rb* gene in the same retinoblast.

2. **Germline/Heritable:** About 40 percent of all retinoblastoma patients have a germline mutation in the *Rb* gene, although only about 7 percent have a positive family history. Therefore, most patients with heritable retinoblastoma are sporadic cases with a new germline mutation [21]. The heritable form of retinoblastoma is associated with multiple, bilateral eye tumors. In addition, these patients are at risk for second primary cancers like osteosarcoma, soft tissue sarcoma and other mesenchymal tumours, brain tumour, lung and bladder cancer and transmission of the disease to their offspring in an autosomal-dominant fashion. About 15 percent of patients with unilateral disease carry a germline mutation, and they are still at risk for second tumors and hereditary transmission [22].

Retinoblastoma gene*:* Rb gene on chromosome 13q14 is a large gene (27 exons spanning 200 kilobases of DNA) which is now known to be mutated in all retinoblastomas, as well as some osteosarcomas and other retinoblastoma-associated cancers [23]. Rb gene is critical for normal cell growth and homeostasis throughout the body. In most tissues, loss of Rb leads to apoptosis (programmed cell death) by triggering the *p53* pathway, thereby preventing malignant transformation. This explains why both the Rb cell cycle pathway and the p53 apoptosis pathway are disrupted in most cancers.

Retinoblastoma protein: The product of Rb gene is a 110-kd nuclear phosphoprotein . Rb protein is central to regulating cell division throughout the body and is pathologically inactivated in the vast majority of all cancers. The Rb protein localizes to the nucleus and can exist in both an active hypophosphorylated form and an inactive hyperphosphorylated form. When active, the Rb protein arrests the cell cycle by blocking the expression of genes involved in DNA synthesis and cell division. When the Rb protein is hyper phosphorylated, these cell cycle genes are unopposed in promoting cell division. Cyclin dependent kinases phosphorylate the Rb protein in a highly regulated manner that normally allows cells to divide only under appropriate physiologic circumstances [24].



RISK FACTORS

1. **Family history:** Risk of retinoblastoma is substantially increased if either of a child's parents had prior retinoblastoma. The risk is more pronounced if the family member had bilateral disease, multifocal intraocular disease or both.

2. **Advanced parental age:** The parents of children who develop sporadic hereditary retinoblastoma tend to be slightly but significantly older age. Such parents are more likely to produce spermatocytes or oocytes with increased chromosomal fragility which lead on to chromosomal deletions or other defects that inactivate retinoblastoma gene [25].

3. **Invitro fertilization:** There is a 5 to 7 fold increase in the risk of developing retinoblastoma in children born of invtro fertilization.

4. Potential mechanism of retinoblastoma tumor development was proposed in response to the observation that spontaneous unilateral retinoblastoma may be more frequent in non-industrialized countries.

   a) **Human papilloma virus:** **T**he increased incidence of non-heritable form of retinoblastoma in tropical regions may possibly be due to viral etiology (Human papilloma virus), that caused pRB inactivation by the oncoprotein HPV E7 [26].

   b) Low folate intake during pregnancy was also postulated to play a role in the risk of retinoblastoma

   c) Mother exposed to insect or garden sprays during pregnancy and x-rays with direct fetal exposure and father employed as a metal worker.

PATHOLOGY

Retinoblastoma probably arises from primordial retinoblasts which have the potential to differentiate along the lines of photoreceptors or Mueller cells.

Macroscopically the tumour can present as one of the following:

1. **Endophytic**: Tumour arises from the inner retina and invades the vitreous. Tumour cells may deposit on the lens, zonules, iris and corneal endothelium, angle and aqueous veins.

2. **Exophytic**: Tumour arises from the outer retinal layer and growing towards the choroid inducing retinal elevation and exudative retinal detachment. Retinal vessels are seen over the surface. It can invade bruch's membrane, ciliary vessels, choroid and orbital nerves [27].

3. **Mixed**: common presentation

4. **Diffuse**: Least common presentation with diffuse growth within the retina with no obvious mass leading to late presentation and difficult diagnosis

5. **Spontaneous regression**: This is due to tumour necrosis, immunological reaction, hormonal influence, tumour cell differentiation and phthisis bulbi [28].

6. **Necrotic:** This occurs due to the rapid growth of tumour tissue and is associated with advanced histological features and therefore poor prognosis.

Microscopically, it consists of three areas. Blue areas representing viable tumour cells, pink areas showing necrosis and purple areas containing dystrophic calcification [29].

Retinoblastoma consists of small- to medium-sized round cells with large nuclei and scant cytoplasm. Well-differentiated tumors may have the following features:

- **Flexner-Wintersteiner rosettes:** it contains abortive rods and cones. Clusters of cuboidal or short columnar cells arranged around a central lumen. The nuclei are displaced away from lumen.

- **Homer-Wright rosettes:** It contains radially arranged tumour cells with neural filaments filling the central space. It represents neuroblastic differentiation. It is characteristic of neuroblastoma and medulloepithelioma but can also be seen in retinoblastoma.

- **Fleurettes:** It show advanced photoreceptor differentiation having bouquet like appearance.

Trilateral retinoblastoma: Bilateral retinoblastoma with pinealoblastoma occurs in 2-3% in bilateral familial retinoblastoma.

Retinocytoma:

These benign tumors were initially called retinoma and spontaneously regressed retinoblastoma. In 1983, the first pathologic description of this benign variant was published and the term "retinocytoma" was proposed. The tumor was composed of neuronal cells showing photoreceptor differentiation, including large number of fleurettes and some glial cells. Retinocytomas have been reported in persons with germline mutations and, when present, have the same genetic implication as a typical retinoblastoma [30].

CLINICAL FEATURES

Clinically, Retinoblastoma begins as a small, transparent lesion in the sensory retina. As the tumour enlarges, it becomes opaque and develops a dilated retinal feeding artery and draining vein, and secondary retinal detachment can occur.

The most common presenting features are leucocoria and strabismus. In advanced intraocular disease, buphthalmos, spontaneous hyphaema, neovascular glaucoma, pseudo hypopyon and orbital cellulitis like picture can occur. In advanced extraocular disease, proptosis and systemic metastasis to bone, meninges, liver, pleura, lymph nodes etc., can occur. Advanced presentation is seen more commonly in less developed countries than in developed countries as per various studies.

Sign or symptom	New York n=900 [31]	AIIMS Delhi n=392 [32]	LVPEI N=46[33]	Eastern India n=42 [34]	North India N=47 [35]	Beijing n=1234 [36]
Leucocoria	56.2	72.2	71	20	17	67.2
Strabismus	23.6	10	6		6.1	4.4
Red eye	7	1.26	2	4	4.5	5.3
Poor vision	5.2	0.25	12	4	-	10.8
Orbital cellulitis	3	0.5	-	5	2.8	1.3
Hyphaema	1	0.25	-	4	-	-
Routine examination	3	1.5	-		-	
Heterochromia	1	0.25	-		-	-
Pseudohypopyon	0.5	0.76	2		-	-
Nystagmus	0.5	-	-		2.8	-
Proptosis	-	13	7	3	68	2.1
Iris nodule	-	0.25	-		-	-
Phthisis bulbi	-	0.5	2	2	-	-

CLASSIFICATION

An ideal classification system for retinoblastoma should include two components: grouping and staging. Grouping is a clinical system of prognosticating organ salvage while staging prognosticates survival [37].

REESE ELLSWORTH CLASSIFICATION :

According to the chance of preserving the eye using external beam radiotherapy:

Group 1 (very favorable for saving [or preserving] the eye)

- 1A: one tumor, smaller than 4 disc diameters (DD), at or behind the equator
- 1B: multiple tumors smaller than 4 DD, all at or behind the equator

Group 2 (favorable for saving [or preserving] the eye)

- 2A: one tumor, 4 to 10 DD , at or behind the equator
- 2B: multiple tumors, 4 to 10 DD, all at or behind the equator

Group 3 (doubtful for saving [or preserving] the eye)

- 3A: any tumor in front of the equator
- 3B: one tumor, larger than 10 DD, behind the equator

Group 4 (unfavorable for saving [or preserving] the eye)

- 4A: multiple tumors, some larger than 10 DD
- 4B: any tumor extending anteriorly (toward the front of the eye) to the ora serrata (front edge of the retina)

Group 5 (very unfavorable for saving [or preserving] the eye)

- 5A: tumors involving more than half of the retina
- 5B: vitreous seeding (spread of tumors into the gelatinous material that fills the eye)

INTERNATIONAL (ABC) CLASSIFICATION SYSTEM[38]

According to the chance of preserving the eye using all modern therapeutic approaches

Group A – Very low risk : Small discrete intraretinal tumours away from the foveola and disc

- All tumours are 3 mm or smaller in greatest dimension, confined to the retina and
- All tumors are located further than 3 mm from the foveola and 1.5 mm from the optic disc

Group B – Low risk : All remaining discrete retinal tumors without seeding

- All tumors confined to the retina not in group A
- Any tumor size and location with no vitreous or subretinal seeding

Group C – Moderate risk : Discrete local disease with minimal focal subretinal or vitreous seeding

- Tumor(s) must be discrete
- Subretinal fluid, present or past without gross seeding, involving up to one quadrant of retina
- Local subretinal seeding, present or past, less than 5 mm from the tumor
- Focal vitreous seeding close to discrete tumor

Group D – High risk : Diffuse disease with significant vitreous and/or subretinal seeding

- Tumor(s) may be massive or diffuse
- Subretinal fluid, present or past, up to total retinal detachment
- Diffuse subretinal seeding, may include subretinal plaques or tumor nodules
- Diffuse or massive vitreous disease, may include “greasy” seeds or avascular tumor or masses

Group E – Very high risk : Presence of any one or more of these poor prognosis features

- Tumor touching the lens
- Neovascular glaucoma
- Tumor anterior to anterior vitreous face involving ciliary body or anterior segment
- Diffuse infiltrating retinoblastoma
- Opaque media from hemorrhage
- Aseptic orbital cellulitis
- Phthisis bulbi

INTERNATIONAL RETINOBLASTOMA CLASSIFICATION:

STAGING SYSTEM –

A substaging according to the histopathological features of enucleated specimens may further help to differentiate patients with intraocular disease.

Stage 0 **:** Patients treated conservatively (subject to presurgical ophthalmologic classifications)

Stage l **:** Eye enucleated, completely resected histologically

Stage II : Eye enucleated, microscopic residual tumor

Stage III : Regional extension

a) Overt orbital disease

b) Preauricular or cervical lymph node extension

Stage IV : Metastatic disease

a) Hematogenous metastasis:

1. single lesion

2. multiple lesions

b) CNS extension:

1. Prechiasmatic lesion

2. CNS mass

3. Leptomeningeal disease

CLINICAL WORKUP

Clinical workup starts with detailed history taking includes presenting complaints, family history and previous treatment if any. Ocular examination includes visual acuity, anterior segment evaluation, and posterior segment examination with dilated pupil upto ora serrata of both eyes. Examination under general anesthesia is mandatory [39].

Computed tomography imaging is useful as an initial diagnostic tool in retinoblastoma. It demonstrates hyperdense intraocular lesion with calcium within the tumor in the vast majority of retinoblastomas, although smaller tumors < 5 mm in thickness may not have detectable calcium. It cannot detect optic nerve invasion, intracranial extension and pinealoblastoma [40].

MRI is the primary mode of imaging for retinoblastoma as it facilitates detection of choroidal, scleral and optic nerve invasion. The lesion is hyperintense in T1 and hypointense in T2 weighed images with respect to vitreous.

B – Scan is used to assist in the diagnosis and to measure tumour size before and after treatment. It appears as an acoustically solid mass with highly reflective foci representing calcification.

Metastatic survey includes physical examination for lymphadenopathy, hepatosplenomegaly or bony swelling. Chest X-ray, peripheral smear, CSF and bone marrow analysis are required. MRI brain and orbit for every six months [41].

TREATMENT

The primary goal of management of retinoblastoma is to save life. Salvage of the organ (eye) and function (vision) are the secondary and tertiary goals respectively [41]. The management strategy depends on the stage of the disease – intraocular retinoblastoma, retinoblastoma with high-risk characteristics, orbital retinoblastoma and metastatic retinoblastoma. Management of retinoblastoma is highly individualized and is based on several considerations - age at presentation, laterality, tumour location, tumour staging, visual prognosis, systemic condition, family and societal perception, and, to a certain extent, the overall prognosis and cost-effectiveness of treatment in a given economic situation.

MANAGEMENT OF INTRAOCULAR RETINOBLASTOMA

A majority of children with retinoblastoma manifest at the stage when the tumor is confined to the eye. About 90-95% of children in developed countries present with intraocular retinoblastoma while 60-70% present at this stage in the developing world [42]. Diagnosis of retinoblastoma at this stage and appropriate management are crucial for life, eye and possible vision salvage. The various treatment modalities available are as follows:

Cryotherapy

It is performed for small equatorial and peripheral retinal tumors measuring up to 4 mm in basal diameter and 2 mm in thickness. Triple freeze thaw cryotherapy is applied at 4-6 week intervals until complete tumor regression [43]. Cryotherapy produces a scar much larger than the tumor. Complications of cryotherapy include transient serous retinal detachment, retinal tear and rhegmatogenous retinal detachment

Laser Photocoagulation

Laser photcoagulation is used for small posterior tumors 4 mm in basal diameter and 2 mm in thickness. The treatment is directed to delimit the tumor and coagulate the blood supply to the tumor by surrounding it with two rows of overlapping laser burns. Complications include transient serous retinal detachment, retinal vascular occlusion, retinal hole, retinal traction, and pre retinal fibrosis.

Thermotherapy

In thermotherapy, focused heat generated by infrared radiation is applied to tissues at subphotocoagulation levels to induce tumor necrosis. The goal is to achieve a slow and sustained temperature range of 40 to 60 degree C within the tumor, thus sparing damage to the retinal vessels. Thermotherapy provides satisfactory control for small tumors - 4 mm in basal diameter and 2

mm in thickness. The major application of thermotherapy is as an adjunct to chemoreduction. The application of heat amplifies the cytotoxic effect of platinum analogues [44]. Greater level of tumour necrosis is achieved with thermotherapy than photocoagulation.

Plaque Brachytherapy

Plaque brachytherapy involves placement of a radioactive implant on the sclera corresponding to the base of the tumor to transsclerally irradiate the tumor. Commonly used radioactive materials include Ruthenium 106 and Iodine 125 [45]. The advantages of plaque brachytherapy are focal delivery of radiation with minimal damage to the surrounding normal structures, absence of cosmetic abnormality because of retarded bone growth in the field of irradiation as occurs with external beam radiotherapy, reduced risk of second malignant neoplasm and shorter duration of treatment. Plaque brachytherapy is indicated in tumors less than 16 mm in basal diameter and less than 8 mm thickness. Advantage of ruthenium over iodine is its improved dose calculation and longer half-life of 6 months.

External Beam Radiotherapy

External beam radiotherapy was the preferred form of management of mod erately advanced retinoblastoma in late 1900s. However with the advent of newer chemotherapy protocols, external beam radiotherapy is being used less often. Presently it is indicated in eyes where primary chemotherapy

and local therapy has failed, or rarely when chemotherapy is contraindicated. The major problems with external beam radiotherapy are the stunting of the orbital growth, dry eye, cataract, radiation retinopathy and optic neuropathy [46]. There is a high 30% chance of developing another malignancy by the age of 30 years in such patients if they are given external beam radiotherapy compared to a less than 6% chance in those who do not receive external beam radiotherapy.

Chemotherapy

Chemoreduction, defined as the process of reduction in the tumor volume with chemotherapy, has become an integral part of the current management of retinoblastoma [47]. Chemotherapy alone is however not curative and must be associated with intensive local therapy. Chemoreduction coupled with focal therapy can minimize the need for enucleation or external beam radiotherapy without significant systemic toxicity [48].

Chemoreduction in combination with focal therapy is now extensively used in the primary management of retinoblastoma. There are different protocols in chemotherapy. The commonly used drugs are vincristine, etoposide and carboplatin, for 6 cycles. Standard dose chemoreduction is provided in ICIOR groups A-C. In high dose chemoreduction, the dose of etoposide and carboplatin is increased. This is indicated in ICIOR groups D tumors [49]. With chemoreduction and sequential local therapy, it is now possible to salvage many an eye and maximize residual vision.

Combination chemotherapy with vincristine sulfate, carboplatin and etoposide phosphate is usually administered in 6 cycles, but up to 13 cycles are sometimes required to control the disease. Cyclosporine has been added to these three agents in some institutions in order to overcome drug resistance. When combined with focal therapy such as laser or cryotherapy, this multimodality approach is generally quite successful for less advanced tumors.

VINCRISTINE:

It is a vinca alkaloid which specifically binds to β-tubulin and blocks its ability to polymerize with α-tubulin and form microtubules. Cells blocked in mitosis undergo changes characteristic of apoptosis. Vincristine sulfate seems to be better tolerated by children than by adults who may experience neurological toxicity. myelosuppression is less common than with vinblastine. Vincristine is given intravenously and precaution should be made to avoid extravasation.

CARBOPLATIN:

Carboplatin (Paraplatin) is a platinum coordinator compound which crosslinks DNA similar to alkylating agents. It is eliminated by renal excretion. Major side effects include nephrotoxicity, ototoxicity, neuropathy, hypomagnesemia, hypersensitivity reactions and hepatotoxcity.

ETOPOSIDE:

Etoposide inhibits DNA and is eliminated via hepatic biotransformation and excretion. Main adverse effects include allergic reactions, hepatotoxicity, CNS toxicity, hypotension, alopecia, acute myelogenous leukemia and mucositis in high doses.

Chemoreduction Regimen and Doses for Intraocular Retinoblastoma

Day 1: Vincristine + Etoposide + Carboplatin

Day 2: Etoposide

Standard dose (3 weekly, 6 cycles): Vincristine 1.5 mg/m22 (0.05 mg/kg for children < 36 months of age and maximum dose < 2mg), Etoposide 150 mg/m (5 mg/kg for children < 36 months of age), Carboplatin 560 mg/m2 (18.6 mg/kg for children < 36 months of age)

High-dose (3 weekly, 6-12 cycles): Vincristine 0.025 mg/Kg, Etoposide 12 mg/Kg, Carboplatin 28 mg/Kg

There are five tumour regression patterns following treatment for retinoblastoma with external beam radiotherapy, chemoreduction, plaque therapy, laser photocoagulation and cryotherapy [50]. These include:

Type 0: complete tumour disappearance leaving no scar

Type 1: tumour regression with complete calcification

Type 2: tumour regression with no calcification

Type 3: tumour regression with partial calcification

Type 4: tumour regression with flat atrophic scar

Enucleation

Enucleation is a common method of managing advanced retinoblastoma. A substantial reduction in the frequency of enucleation has occurred in the late last century [51]. Concurrently, there has been an increase in the use of alternative eye- and vision-conserving methods of treatment. Primary enucleation continues to be the treatment of choice for advanced intraocular retinoblastoma with neovascularization of iris, secondary glaucoma, anterior chamber tumor invasion, tumors occupying >75% of the vitreous volume, necrotic tumors with second ary orbital inflammation, and tumors associated with hyphema or vitreous hemorrhage where the tumor characteristics cannot be visualized, especially when only one eye is involved[52].

Special Considerations for Enucleation in Retinoblastoma :

- Minimal manipulation
- Avoid perforation of the eye
- Harvest long (> 15 mm) optic nerve stump

- Inspect the enucleated eye for macroscopic extraocular extension and optic nerve involvement
- Harvest fresh tissue for genetic studies
- Avoid biointegrated implant if postoperative radiotherapy is necessary.

Histopathologic High-risk Factors Predictive of Metastasis:

- ✓ Anterior chamber seeding
- ✓ Iris infiltration
- ✓ Ciliary body infiltration
- ✓ Massive choroidal infiltration
- ✓ Invasion of the optic nerve lamina cribrosa
- ✓ Retrolaminar optic nerve invasion
- ✓ Invasion of optic nerve transection
- ✓ Scleral infiltration
- ✓ Extrascleral extension

The reported occurrence of anterior chamber seeding (7%), massive choroidal infiltration (12-23%), invasion of optic nerve lamina cribrosa (6-7%), retrolaminar optic nerve invasion (6-12%), invasion of optic nerve transection (1-25%), scleral infiltration (1-8%), and extrascleral extension (2-13%), widely vary even in developed countries. Vemuganti and associates have reported that 21% of the 76 eyes enucleated for advanced retinoblastoma in India had anterior chamber seeding, 54% had massive choroidal

infiltration, 46% had optic nerve invasion at or beyond the lamina cribrosa and 7% had scleral infiltration or extrascleral extension.12 It is apparent that the incidence of histopatho logic risk factors is strikingly high in developing countries compared to the published data from developed countries.

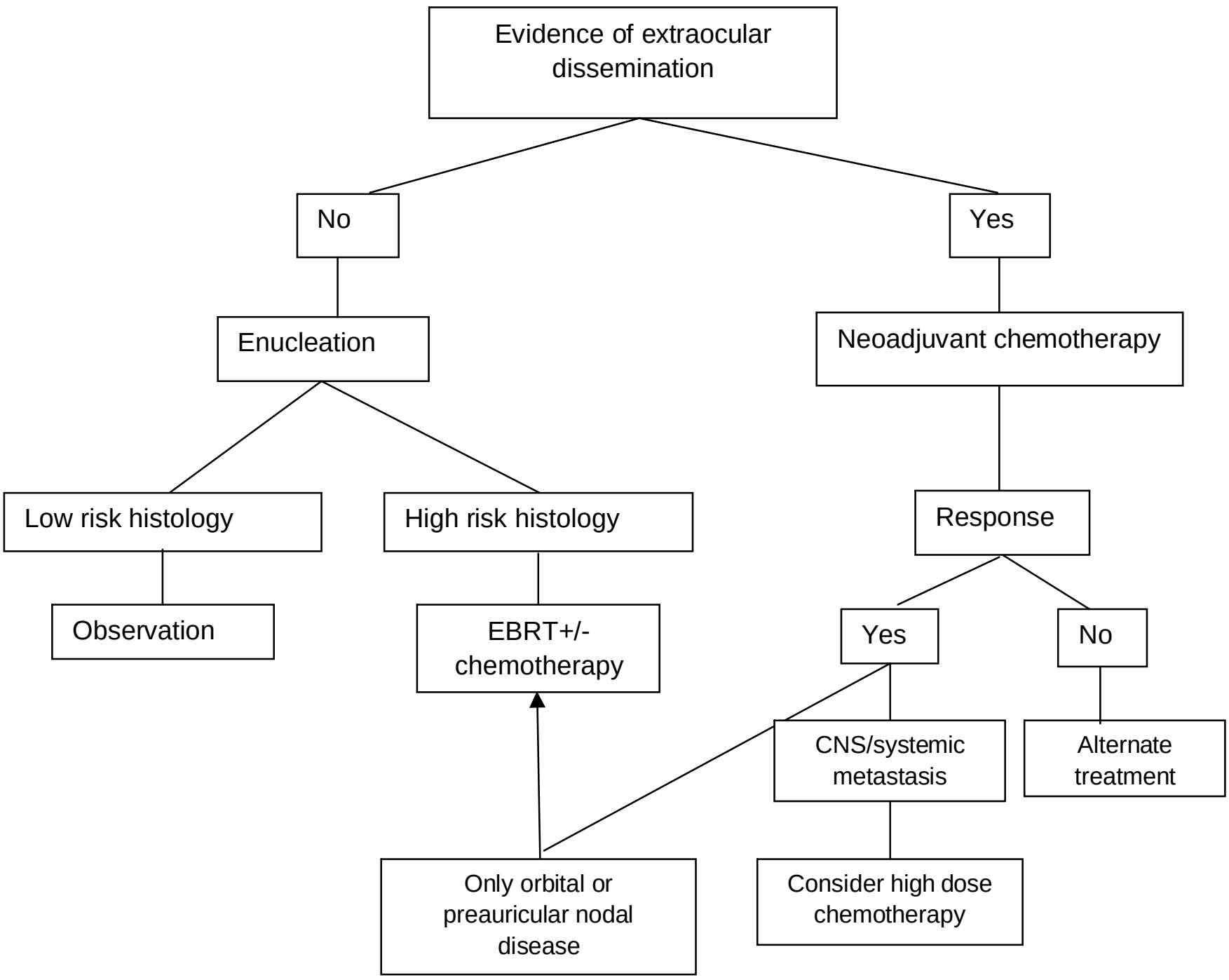
Adjuvant Therapy

Studies on the efficacy of adjuvant therapy to minimize the risk of metastasis initiated in the 1970s were marked by variable results and provided no firm recommendation[53]. Recent studies show that the incidence of metastasis was 4% in those who received adjuvant therapy compared to 24% in those who did not. The study found that administration of adjuvant therapy significantly reduced the risk of metastasis in patients with high-risk histopathologic characteristics [54]. Current practice is to administer 6 cycles of a combination of carboplatin, etoposide and vincristine (identical to the protocol used for chemoreduction of intraocular retinoblastoma) in patients with histopathologic high-risk characteristics [55]. All patients with extension of retinoblastoma up to the level of optic nerve transection, scleral infiltration, and extrascleral extension should receive high dose chemotherapy for 12 cycles and fractionated 4500 to 5000 cGy or bital external beam radiotherapy.

Follow-up Schedule

The usual protocol is to schedule the first examination 3–6 weeks after the initial therapy. In cases where chemoreduction therapy has been administered, the examination should be done every 3 weeks with each cycle of chemotherapy. Patients under focal therapy are evaluated and treated every 4-8 weeks until complete tumor regression. Following tumor regression, subsequent examination should be 3 monthly for the first year, 6 monthly for three years or until the child attains 6 years of age, and yearly thereafter.

MANAGEMENT OF ADVANCED RETINOBLASTOMA



IMPLANT PLACEMENT IN ANOPHTHALMIC SOCKET

Enucleation in children has been associated with contraction of socket especially at less than 1 year of age. Radiotherapy given for retinoblastoma causes arrest in the bone development leading to anophthalmic socket syndrome causing soft tissue loss and contracted socket [56]. Placement of an orbital implant following enucleation for retinoblastoma is the current standard of care. The orbital implant promotes orbital growth, provides better cosmesis and enhances prosthesis motility. The implants could be non-integrated (polymethyl methacrylate or silicon) or bio-integrated (hydroxyapatite or porous polyethylene).

Placement of a biointegrated implant is generally avoided if post-operative adjuvant radiotherapy is considered necessary. Porous implants like hydroxyapatite can be used after 15 years of age. Although most implants structurally tolerate radiotherapy well, implant vascularization may be compromised by radiotherapy thus increasing the risk of implant exposure. Use of myoconjunctival technique and custom ocular prosthesis have optimized prosthesis motility and static cosmesis. Use of non-biodegradable implants like silicon and PMMA with biological tissue wraps helps in improving motility. Wrapping material can be donor sclera, bovine pericardium or fascia lata. They are not affected by irradiation and can be changed with age. Dermis fat graft is ideal for children as it appears to grow

after implantation [57]. This growth of the implant may help stimulate orbital growth, potentially leading to more symmetry between the involved and uninvolved sides. It maintains the volume of the socket.

Determining Implant Size Based on the Size of the Natural Eye

Diameter of natural eye (mm)	Volume of natural eye (ml)	Volume of artificial eye (ml)	Volume deficit remaining (m)	Diameter of implant to use if unwrapped (mm)	Diameter of implant to use if wrapped (mm)
20.0	4.19	2.5	1.69	15.0	13.5
20.5	4.51	2.5	2.01	15.5	14.0
21.0	4.85	2.5	2.35	16.5	15.0
21.5	5.21	2.5	2.71	17.5	16.0
22.0	5.58	2.5	3.08	18.0	16.5
22.5	5.97	2.5	3.47	19.0	17.5
23.0	6.37	2.5	3.87	19.5	18.0
23.5	6.80	2.5	4.30	20.0	18.5
24.0	7.24	2.5	4.74	21.0	19.5
24.5	7.70	2.5	5.20	21.5	20.0
25.0	8.18	2.5	5.68	22.0	20.5
25.5	8.69	2.5	6.19	23.0	21.5
26.0	9.21	2.5	6.71	23.5	22.0

PART 2

AIMS AND OBJECTIVES

The aims of this study were to analyse:

- Age incidence
- Sex distribution
- Laterality
- Modes of presentation
- Time lag between onset of symptoms and presentation
- Staging
- Management and follow-up of cases diagnosed as Retinoblastoma

MATERIALS AND METHODS

This study was a prospective study conducted at Regional Institute of Ophthalmology, Govt. Ophthalmic Hospital from May 2009 to November 2011. All the children who presented to our institution with features suggestive of Retinoblastoma were included in the study after confirmation of diagnosis. 28 consecutive patients (36 eyes) were included in the study.

Detailed clinical history was obtained regarding the presenting complaints like appearance of “amaurotic cats’ eye”, pain, watering, redness, protrusion of eyes, defective vision etc. The duration and progression of these features and time lag between onset and diagnosis was obtained. Family history regarding consanguinity, health of the siblings and occurrence of similar features in other family members is recorded.

Ocular examination included visual acuity, slit lamp examination. Detailed fundus evaluation after total mydriasis under general anaesthesia was done. Investigations like B-Scan, Computed Tomography/MRI imaging of orbit and brain was done. General examination to look for lymphadenopathy, hepatomegaly and bony swellings was done. Metastatic work-up included peripheral smear, bone marrow aspiration, CSF analysis, X-ray chest and USG abdomen.

Enucleated eyes were subjected to histopathological evaluation and findings recorded. Children were followed up every 1 month until completion of treatment and then every 3 months and fundus evaluation and examination of empty socket. B-Scan was done every 3 months. CT/MRI was repeated every 6 months.

RESULTS AND ANALYSIS

In this study, a total of 28 cases were evaluated for the following:

Table 1:

AGE INCIDENCE

Age at presentation	No. of cases	Percentage
< 1 yr	7	25
1-3 yrs	15	53.57
>3yrs	6	21.43

Of the 28 cases examined, 53.57% were in the age group of 1 to 3 years followed by 25% below 1 year and 21.43% above 3 years. The youngest child was 1 month old with bilateral Retinoblastoma.

TABLE 2:

SEX DISTRIBUTION

Sex	No. of cases	Percentage
Males	13	46.43
Females	15	53.57

In our study, there were 13(46.43%) males and 15(53.57%) with the male to female ratio of 0.82.

TABLE 3:

LATERALITY

Laterality	No. of cases	Percentage
Unilateral		
Right eye	9	32.14
Left eye	11	39.29
Bilateral	8	28.57

TABLE 4:

MEAN AGE AT PRESENTATION ACCORDING TO LATERALITY

Laterality	No. of cases			Percentage	Mean age at presentation (months)
	<1 yr	1-3yrs	>3yrs		
unilateral	2	14	4	71.43	28.95
Bilateral	5	2	1	28.57	16.88

Retinoblastoma was unilateral in 20 cases (71.43%) and bilateral in 8 patients (28.57%). Mean age at presentation of bilateral retinoblastoma was 16.88 months.

TABLE 5:

MODE OF PRESENTATION

Sign	No. of cases	Percentage
Leucocoria	18	64.29
Leucocoria+red eye	2	7.14
Proptosis	2	7.14
Leucocoria+proptosis	2	7.14
Orbital cellulitis	1	3.57
Red eye	1	3.57
Red eye after trauma	1	3.57
Pseudohypopyon	1	3.57

Leucocoria was the commonest presentation in 64.29% of patients followed by leucocoria with red eye, proptosis and leocucuria with proptosis in 7.14% of patients.

TABLE 6:

TIME INTERVAL BETWEEN NOTICING OF

FIRST SYMPTOM AND DIAGNOSIS

First symptom	Median lag time in weeks
Leucocoria	2 (1-5)
Leucocoria+red eye	8(4-24)
Leucocoria+proptosis	10.5(8-13)
Proptosis	11.5(10-13)
Orbital cellulitis	10
Red eye	2.5 (1-4)

The mean time lag between onset of symptom and diagnosis was 4.5 weeks.

TABLE 7:

CLASSIFICATION OF THE TUMOUR

Group	No. of eyes	Percentage
A	-	-
B	-	-
C	2	5.56
D	23	63.88
E	11	30.56

About 94.44% of eyes (33) presented with advanced stage of disease. Only 3 eyes were in the favorable staging.

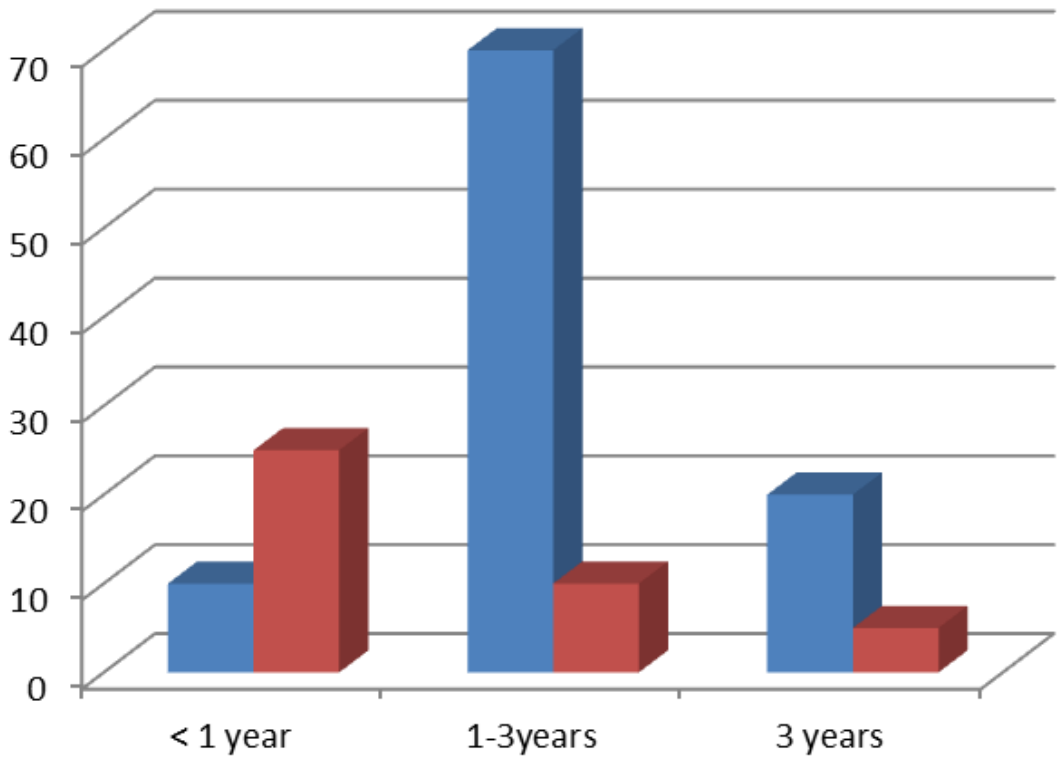
TABLE 8:

CALCIFICATION IN ULTRASOUND AND CT

Calcification	Ultrasound		CT	
	Eyes	%	Eyes	%
Present	34	94.44	34	94.44
Absent	2	5.56	2	5.56

Calcification was equally detected by both ultrasound and CT in all cases except 2 eyes in which both the imaging modalities could not identify calcification.

AGE AT PRESENTATION



MODE OF PRESENTATION

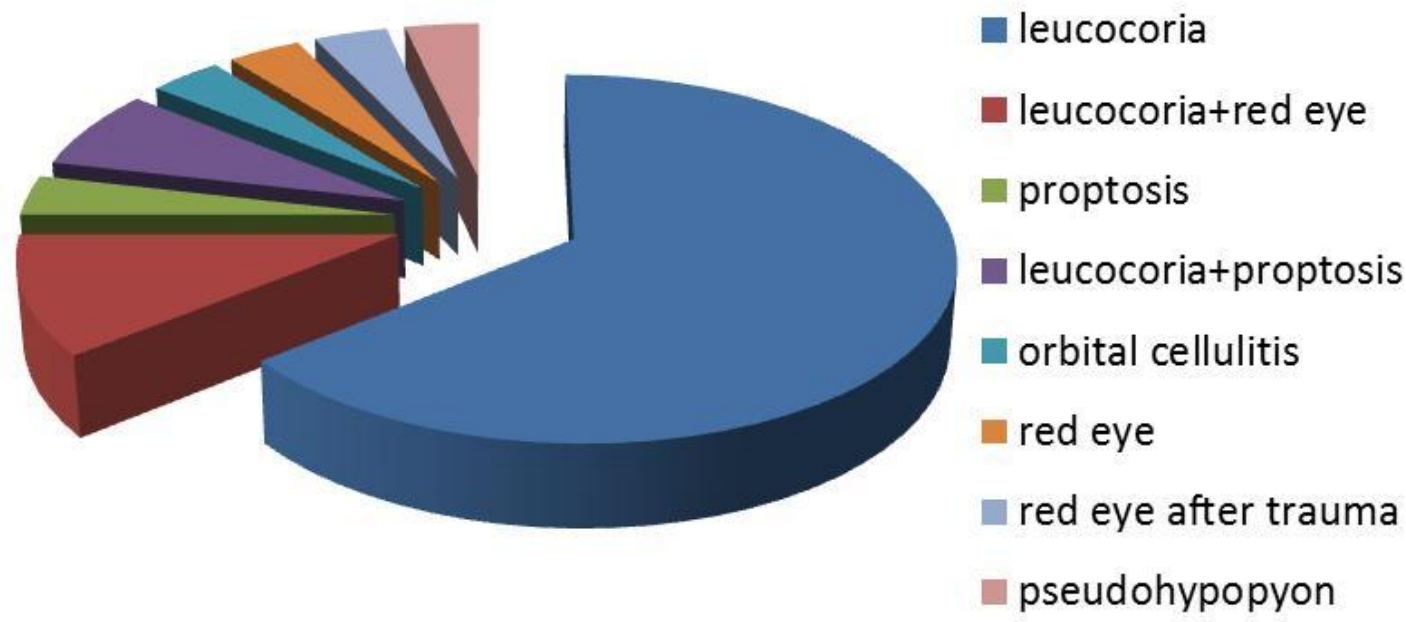


TABLE 9:

EVIDENCE OF SPREAD OF TUMOUR ON MRI

Features	No.of eyes	Percentage
Intraocularr	29	80.55
Optic nerve invasion	3	8.33
Extraocular extension	2	5.56
Intracranial metastasis	2	5.56

The tumour was confined to the globe in 80.55% of patients but the rest showed evidence of spread.

TABLE 10:

MODE OF TREATMENT

Treatment	No. of patients	Percentage
Enucleation	10	35.70
Enucleation followed by chemotherapy	8	28.57
Enucleation followed by Chemotherapy+Radiotherapy	4	14.28
Chemotherapy	2	7.14
Chemotherapy+Radiotherapy Followed by enucleation	2	7.14
Refused treatment	2	7.14

Majority of the patients (85.71%) had to undergo enucleation due to the late stage of presentation.

TABLE11:

HIGH RISK HISTOLOGICAL FEATURES

HPE	Median age at presentation (months)	No. of eyes (n=26)	Percentage
No risk factors	24	15	57.69
Choroidal invasion	24	5	19.23
Scleral and Optic nerve invasion	42	3	11.53
Optic nerve + choroidal invasion	36	1	3.85
Optic nerve invasion	96	1	3.85
Iris infiltration	36	1	3.85

Of the 26 eyes enucleated, high risk histological features which could lead to metastasis was found in 11 eyes (42.31%) with Choroidal invasion being the most common feature (19.23%).

TABLE 12:

ORBITAL IMPLANT

Implant	Time of implant	No. of eyes (n=26)	Percentage
No implant		19	73.08
PMMA	Primary	4	15.38
PMMA	Secondary	2	7.69
Dermis fat	Secondary	1	3.85

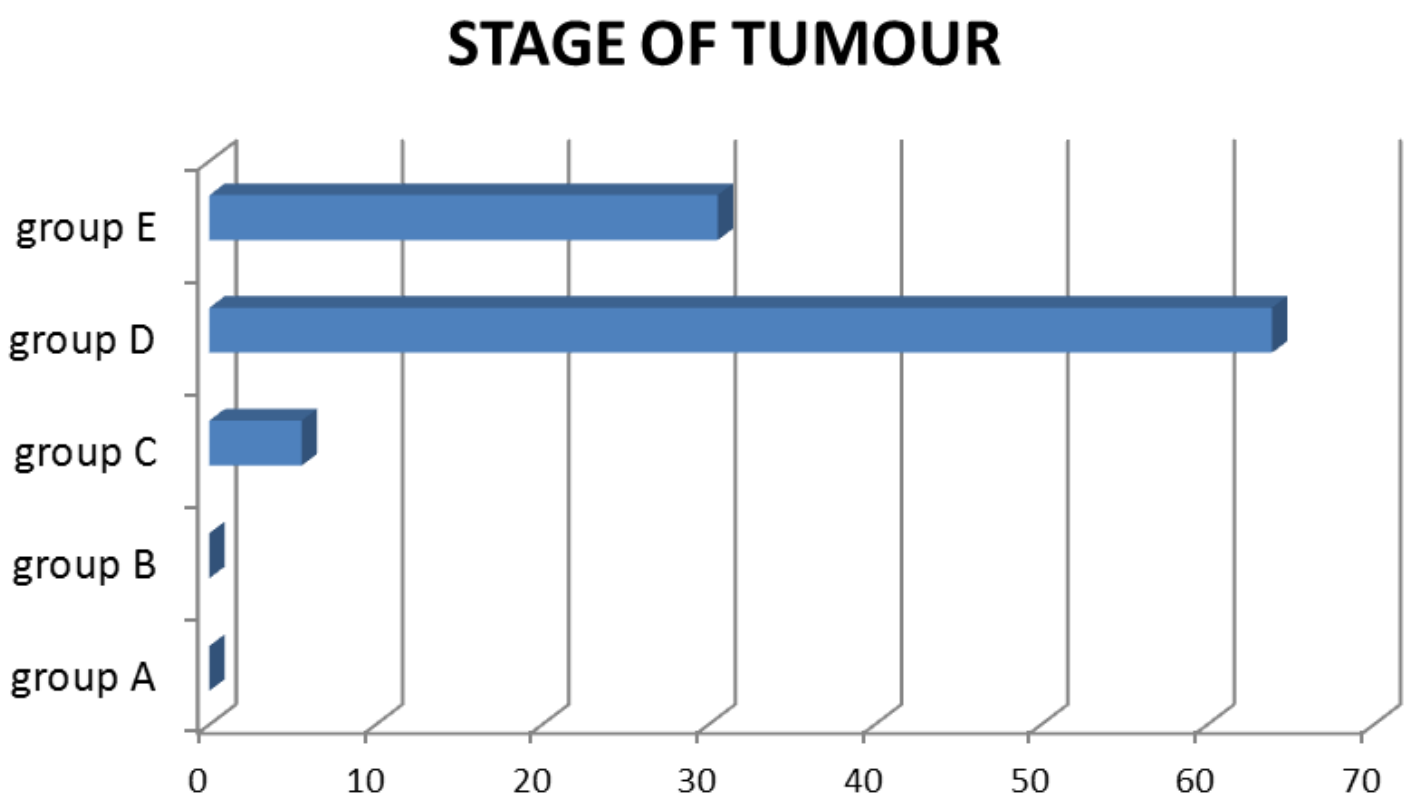
Out of the 26 enucleations, 7 eyes (26.92%) were replaced by implants.

TABLE 13:

STAGE OF RETINOBLASTOMA

Stage		No. of patients	Percentage
0		2	7.69
l		16	61.54
ll		4	15.38
lll	a	1	3.85
	b	-	-
lV	a	1	3.85
	b	2	7.69

Out of 26 patients treated, sub staging showed 61.54% of patients in stage l in whom enucleation had been done and completely resected histologically.


STAGE OF TUMOUR
group E
group D
group C
group B
group A
0
10
20
30
40
50
60
70

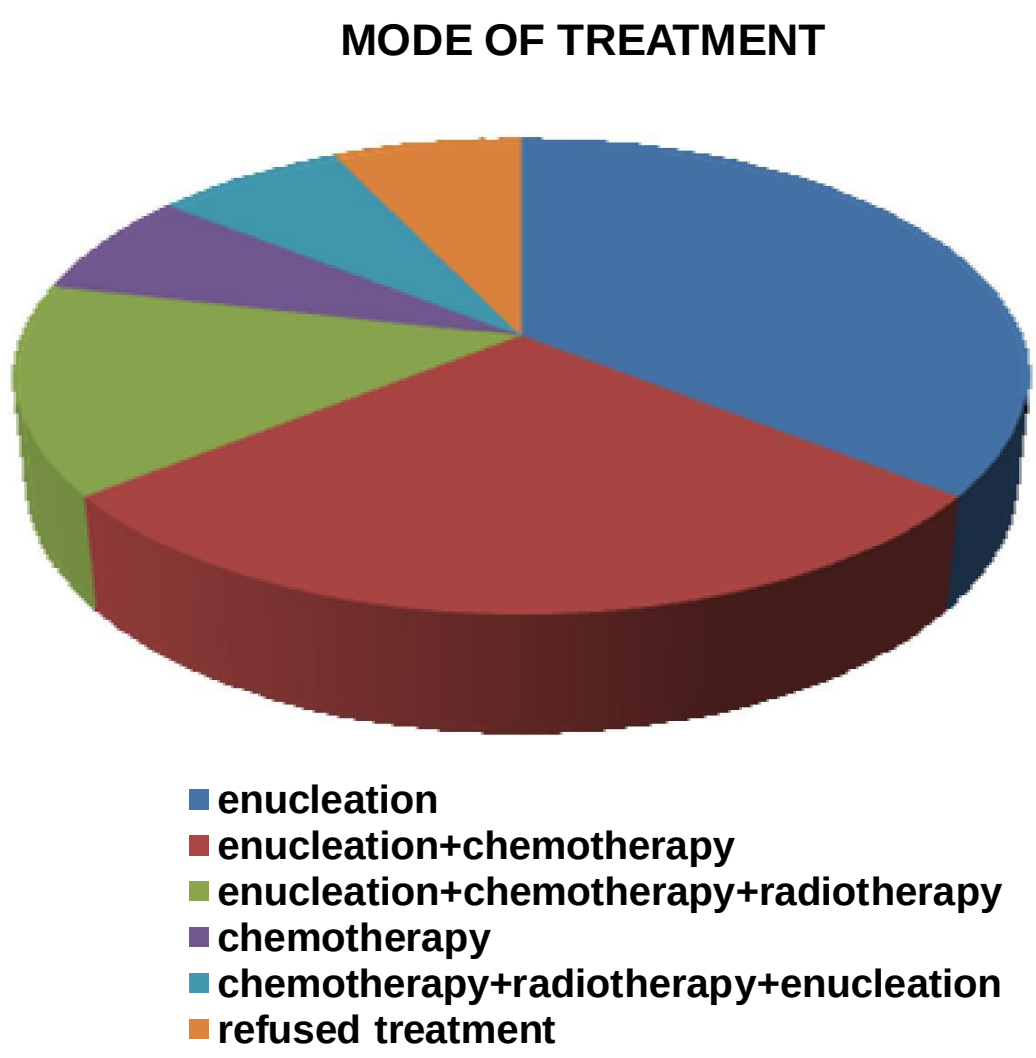
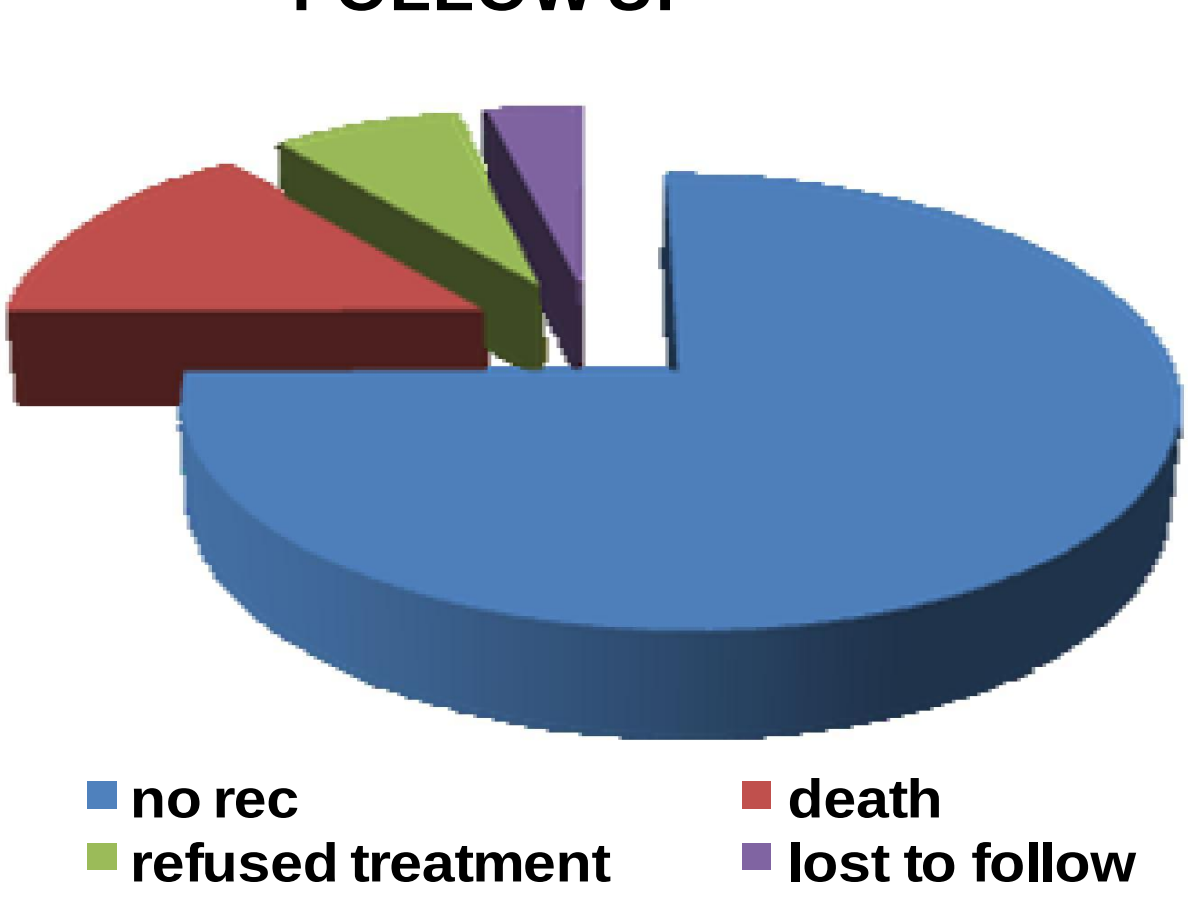

MODE OF TREATMENT
enucleation
enucleation+chemotherapy
enucleation+chemotherapy+radiotherapy
chemotherapy
chemotherapy+radiotherapy+enucleation
refused treatment

TABLE 14:

FOLLOW UP OF CASES:

Outcome	No. of cases	Percentage
No recurrence	21	75
Death	4	14.29
Refused treatment	2	7.14
Lost to follow-up	1	3.57

Cases were followed up monthly during the initial 3 months and 6 monthly thereafter with a minimum of 3 months during study period. No recurrence was seen in 21 patients. 4 patients died during the study period.



DISCUSSION

In our study, age group of the patients was from 1 month to 8 years with a mean of 26.25 months. Most of the patients presented within 3 years of age accounting for 78.57% of cases. Our study was similar to that of Abramson et al [31]. Studies done in India showed similar findings. A study done by Shanmugam et al showed mean age at presentation to be 23.98+/-23.37 months [58].

In our study, there were 13(46.43%) males and 15(53.57%) with a ratio of 0.82. Studies by Azar et al showed no significant difference [59]. While those by Alegria et al [60] and Kaimbo et al showed male to female ratio of more than 1. some studies have shown female preponderance like that of Mukhopadyaya et al [61].

Most of the patients presented with unilateral Retinoblastoma, accounting for 71.43% (20 cases) of cases with a mean age of 28.95 months while patients with bilateral disease presented at an earlier age with a mean of 16.88 months with the youngest being 12months of age. Similar earlier presentation of bilateral Retinoblastoma has been seen in study by Junyang Zhao et al (study of 470 patients) in which unilateral disease presented at mean age of 27 months while bilateral at 15 months [36].

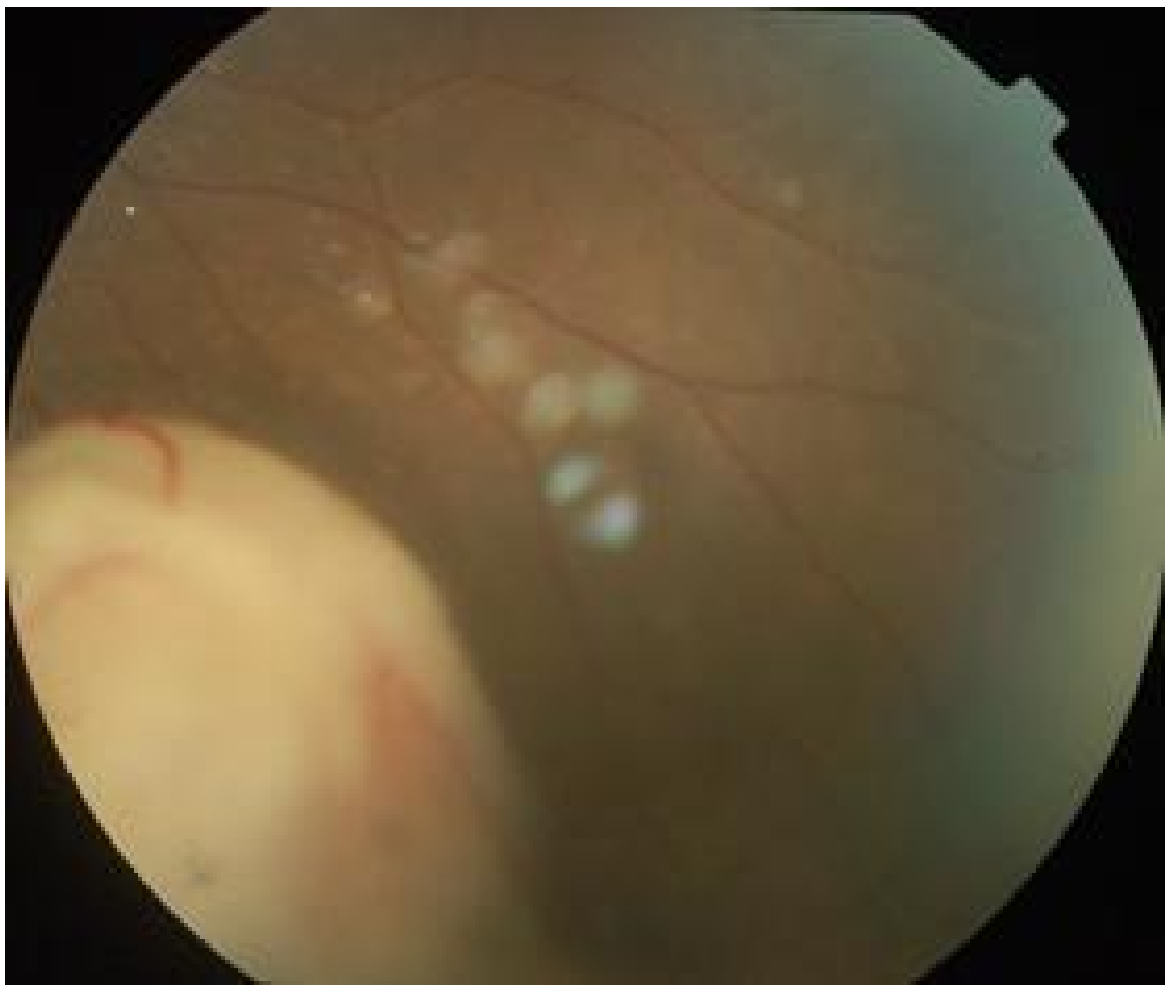


Fig.1 Fundus photograph showing endophytic lesion with vitreous seeding in Group C

Fig.2 Clinical photograph showing leucocoria in a case of bilateral retinoblastoma

Fig.3 Clinical photograph showing secondary glaucoma

Fig.4 Clinical photograph showing extraocular extension of retinoblastoma

Leucocoria was the most common presenting feature accounting for 64.29% of cases. Similar observations have been seen in various studies in New York, Finland, Beijing [31, 36]. Studies in India also had leucocoria as most common presenting feature. In all the studies more than 50% of patients had leucocoria. Strabismus was not the presenting sign in our study but was one of the significant features in studies by Abramson et al and Honavar et al [31, 33].

Though leucocoria was seen by parents in 14.28% of patients, they were brought to the ophthalmologist only after development of proptosis and red eye. In one patient red eye was attributed to the trauma while leucocoria was unnoticed. This highlights the lack of awareness of parents in identifying the condition. Therefore it is important to educate the public and improve the awareness among health care providers especially pediatricians.

Proptosis, pseudohypopyon and orbital cellulitis which suggest advanced stage at presentation was seen in 21.02% of patients. These findings have been found in studies of developing countries while in Nepal [62], proptosis is the most common presentation. But in studies from New York[31] and Philadelphia have recorded fewer patients with advanced features accounting for less than 10% which necessitates the need for protocol for screening of new born and infants periodically for retinoblastoma.

The time lag between onset of signs and diagnosis was least in patients with leucocoria (2weeks) as it is the most common presentation of retinoblastoma while proptosis had the maximum time lag of 11.5 weeks. The overall median lag was 4.5weeks. Our study showed a statistically significant correlation (p=0.001) between presenting signs and the time lag between onset and diagnosis. Atypical presentation like red eye, orbital cellulitis and proptosis have been associated with delayed diagnosis.

Out of the 36 eyes, all were above group C of International classification at the time of presentation with advanced stage being 94.44% of eyes. Presentation at advanced stage has been seen in studies of developling countries. Study by Sahu et al [34] showed all patients to be in the stage v of Reese Ellsworth classification and that by Junyang et al [36] showed 84% of eyes in advanced stage of disease. This correlates with our study. Only two patients, who had advanced disease in one eye presented with group C in the other. Hence enucleation was the most common modality of treatment in our study.

Calcification was not present in both B-Scan and CT in two cases. All other patients had calcification on both the imaging modalities. Diffuse type of growth was seen in these patients.

Evidence of spread of the tumour on MRI was seen in 18.45% of eyes of which optic nerve invasion was most common accounting for 8.33% of cases followed by intracranial metastasis and extraocular spread in 5.56% each. These findings were not seen in CT imaging. Though calcification is one of the most important diagnostic features of retinoblastoma which is evident on CT, evaluation of extension and metastasis is possible only with MRI imaging.

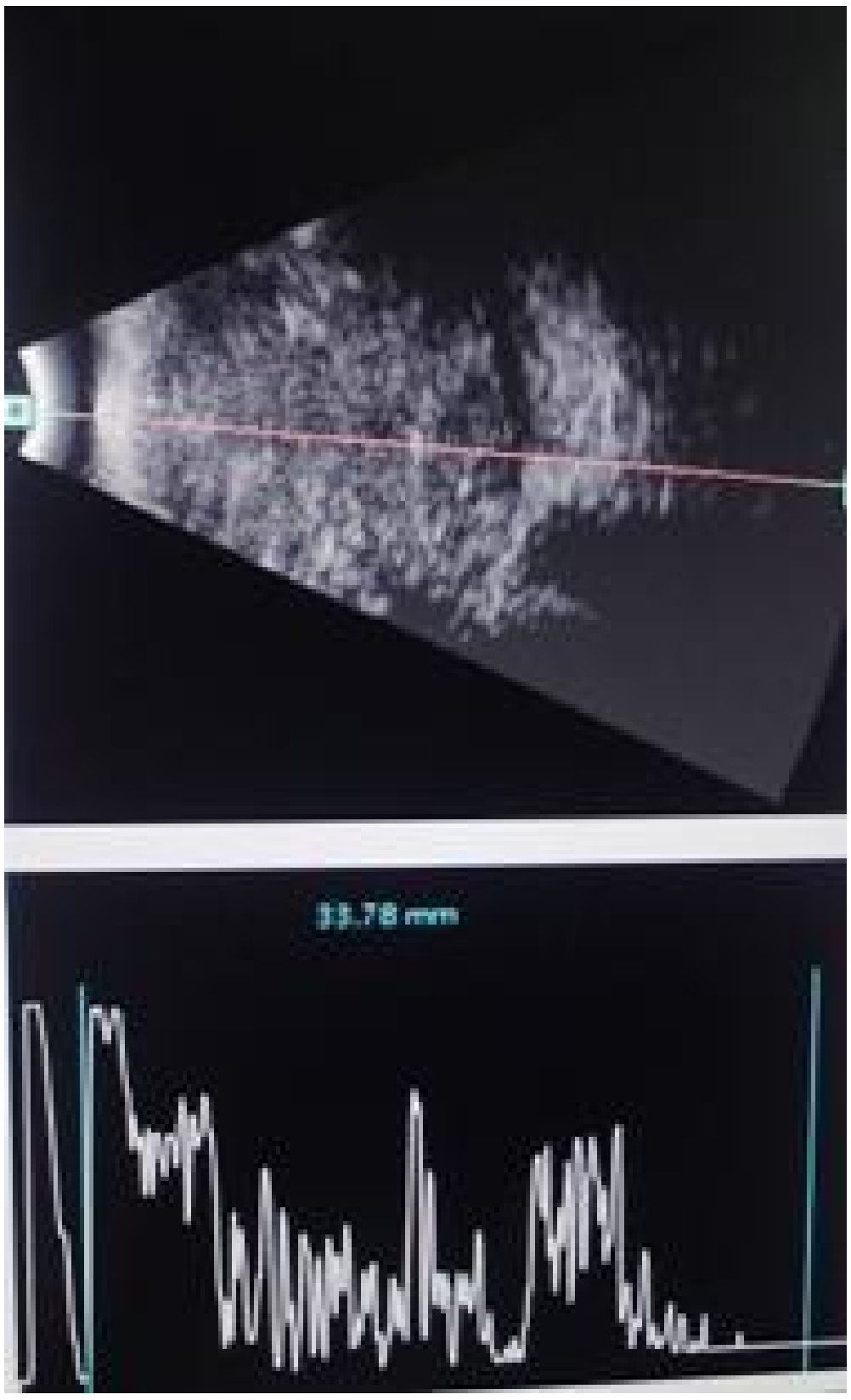


Fig.5 B-Scan image showing moderate intense echoes throughout vitreous cavity with few high intense echoes with corresponding high spike suggesting calcification

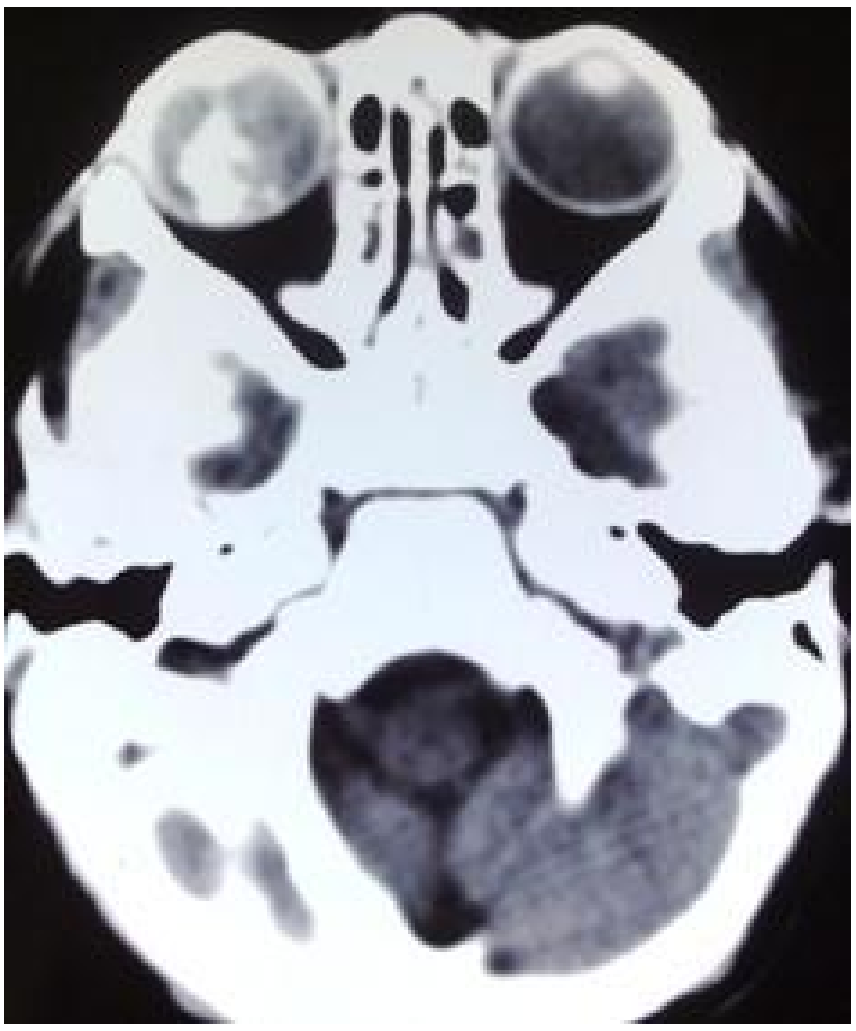


Fig.6 CT image showing intraocular calcification suggestive of retinoblastoma

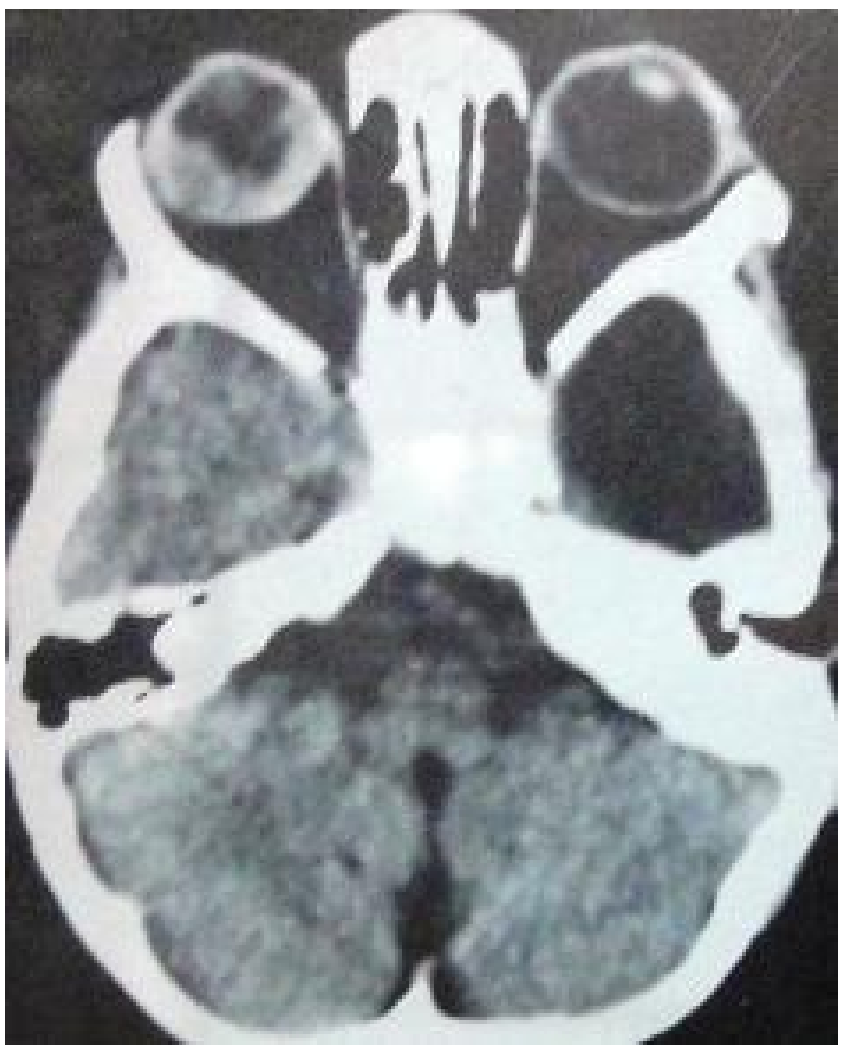


Fig.7 CT image showing diffuse infiltrating lesion without calcification

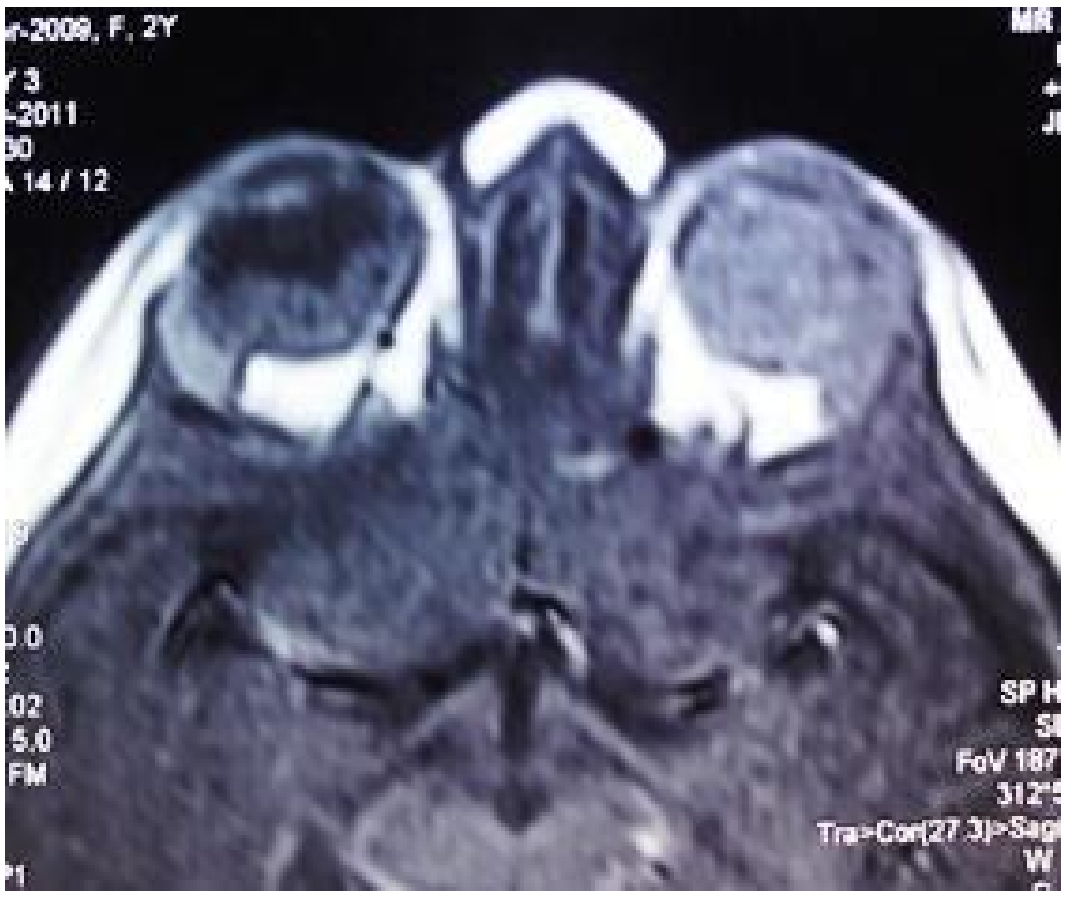


Fig.8 MRI image showing hyperintensity on T1 and hypointensity on T2 in a patient with bilateral retinoblastoma

Majority of our patients underwent enucleation (78.57%) with two patients undergoing bilateral enucleation which correlates with studies of both developed and developing countries in which enucleation has been the primary modality of treatment like that by Honavar et al [33] in which 52% of eyes were enucleated while that by Essuman et al [63] showed at least one eye enucleated in all patients. Enucleation followed by chemotherapy (25%) was given in patients who showed high risk histological characteristics in order to prevent systemic metastasis. Chemotherapy and radiotherapy were given after enucleation (14.28%) as the cut end of optic nerve showed tumour infiltration or when there was extra scleral spread.

In 1 patient, there was no tumour regression with chemotherapy and radiotherapy, so the eyes had to be enucleated. Parents of 2 patients refused treatment due to fear of cosmetic disfigurement. Both were female children with bilateral disease who needed enucleation as they were in group D and E.

Out of the 8 patients with bilateral retinoblastoma, no recurrence during study period was seen in 3 patients. Refusal for treatment and death was seen in two patients each. One patient in whom enucleation was done in one eye and started on chemotherapy and radiotherapy for the other eye was lost to follow-up.

Classification system following treatment for the tumour showed 61.54% of patients were in stage I, though eye salvage was not possible; they had reduced risk for metastasis and recurrence. But in 15.39% of eyes had developed metastasis or had high risk features.

Fig.9 Gross picture showing entire vitreous cavity filled with the tumour with calcification

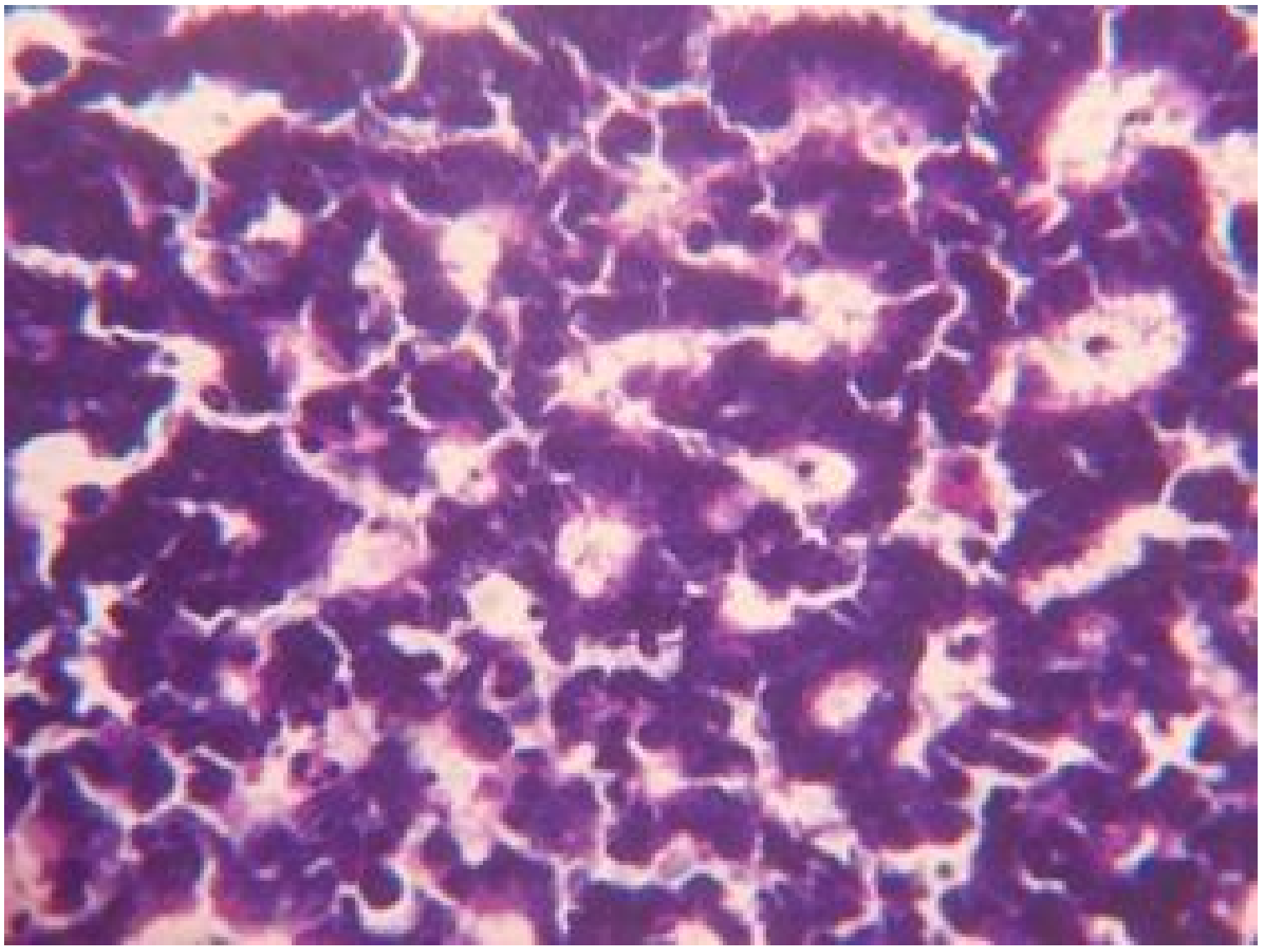


Fig.10 Microphotograph showing Flexner Wintersteiner rosettes.

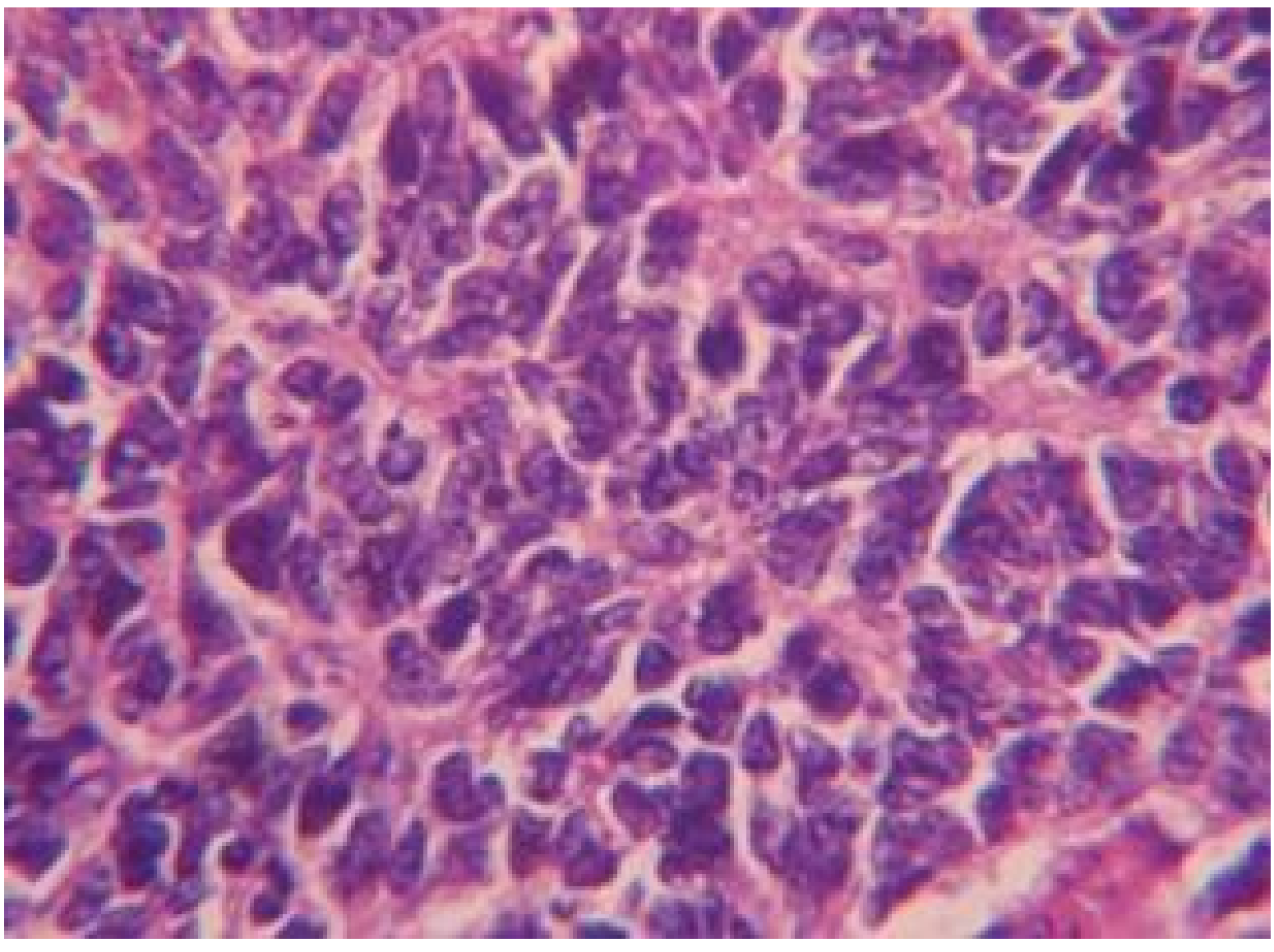


Fig.11 Microphotograph showing Homer Wright rosettes

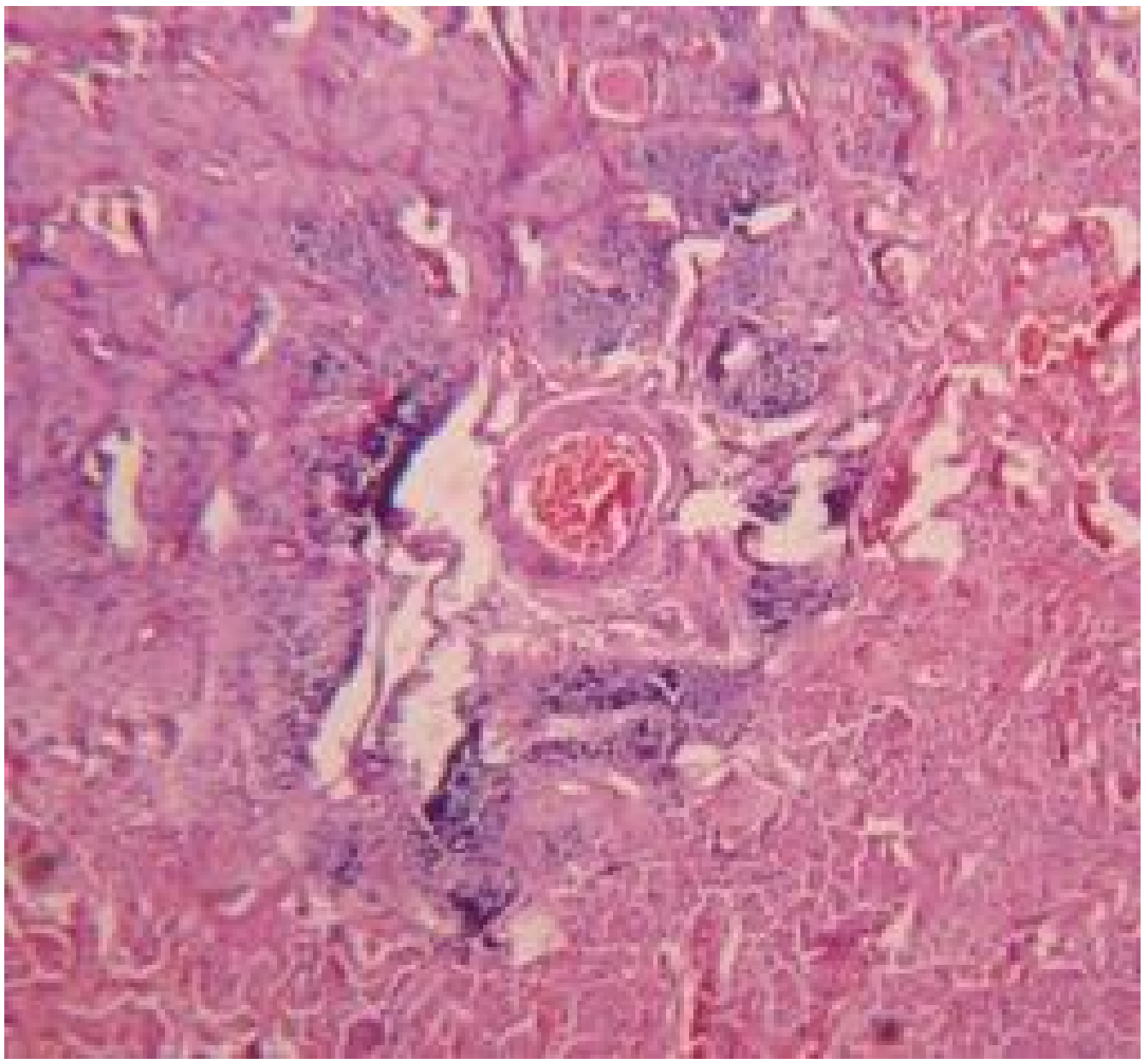


Fig.12 Microphotograph showing optic nerve invasion by the tumour

Fig.13 Clinical photograph showing anophthalmic socket

Fig.14 Clinical photograph after dermis fat graft and prosthesis placement

Fig.15 Clinical photograph after enucleation and placement of primary PMMA implant

Fig.16 Clinical photograph after placement of prosthesis

Orbital implant was placed in 26.92% of eyes as a primary or secondary procedure as other parents were not willing for the procedure. PMMA with donor sclera wrapping was done as primary and secondary procedure in 4 (15.38%) and 2 (7.69%) eyes respectively. Dermis fat graft was placed in 1 (4%) eye as a second stage procedure. One patient in whom secondary PMMA implant was placed after bilateral. The patients had no other complications and there was good cosmetic outcome in all patients. However these patients have to be followed up regularly for any complication or recurrence. Out of the eyes in which implant was not placed, 52.63% showed evidence of extraocular spread or optic nerve invasion while in the rest the parents were not willing for it.

High risk histological features were seen in 42.31% of eyes enucleated of which choroidal invasion was most common showing advanced stage of presentation in these patients. Occurance of these high risk features correlated with greater age at presentation. Median age at occurance of choroidal invasion was 24months, while that of other features was > 30 months similar to study by Gupta et al [64]. Late stage at presentation has been associated with high risk characteristics. These patients have been associated with systemic metastasis and increased mortality. The survival rate among 11 patients with high risk features was 72.72% while it was 100% in patients (14) without them.

Out of the 28 patients, no recurrence was seen in 75% of cases during the study period. Death during the study period occurred in 14.29% (4 patients) of patients of which one patient had advanced bilateral disease and three other patients had metastasis in the form of CNS involvement in two and iliac bone secondaries in one. Studies show improved survival rates in developed countries. Study by Broaddus et al [65] observed the survival rate to be 96.5% in United States while it was 69.62% in study by masood et al [66] in Iran which is similar to our study. Chennai has recorded least survival rate when compared to other cities according to population based cancer registry with a mortality rate of 48% while it is more than 60% in other cities. In our study, 3.57% (1 patient) of patients was lost to follow up while on treatment for secondaries with chemotherapy and radiotherapy.

SUMMARY

A total of 28 retinoblastoma patients and 36 eyes were studied over a three year period for age at presentation, sex, laterality, presenting signs, time lag between symptom onset and diagnosis. All patients were subjected to detailed clinical evaluation and investigations for staging of the disease. The treatment of these patients was recorded.

- In our study, most patients presented within 3years of age accounting for 78.57% of cases ranging from 1 month to 8 years of age

- It was seen that the mean age at presentation was 28.95 months in unilateral and 16.88 months in bilateral retinoblastoma.

- There was a slight female preponderance with male to female ratio being 0.82.

- Leucocoria was the most common presenting feature accounting for 64.29% of cases.

- A significant percentage of patients (28.57%) showed advanced stage of presentation like proptosis, secondary glaucoma and orbital cellulitis.

- The median time lag between onset of symptoms and diagnosis was 4.5 weeks with least for leucocoria and maximum for proptosis.

- 94.44%of patients presented with high and very high risk disease (group D and E of International Classification System) making eye salvage difficult. This highlights the need for effective mass education and screening strategies which could help in early diagnose and treatment

- 85.71% of our patients underwent enucleation which was the most common treatment given. Additional chemotherapy with radiotherapy was needed in patients with high risk histological characteristics which was present in 36% of enucleated eyes.

- Sub staging of Retinoblastoma in our study showed that out of 61.54% of patients in stage l in which enucleation had been done and completely resected histologically.

- Orbital reconstruction in anophthalmic socket should be done with non-biointegrated implant in all patients to improve the cosmosis and for social rehabilitation.

- Though leucocoria is the most common presentation, understanding the other modes of presentation is important for timely diagnosis because survival of children is highly dependent on the degree of advancement of the disease.

- All children should undergo RED REFLEX TESTING as recommended by American Academy of Pediatrics Policy 2008 for new born, infants and children upto 5 years of age by the pediatrician or health care provider during every visit and referred promptly to an ophthalmologist in case of abnormalities detected. This has been associated with decrease in extraocular and systemic metastasis thereby improving the survival rate. Eye salvage is difficult at this stage.

- Dilated fundus examination of children every 3 months upto 5 years of age by an ophthalmologist is necessary in order to detect early lesions before the onset of leucocoria so as to save the eye and improve vision.

CONCLUSION

- Retinoblastoma has excellent prognosis for survival, eye salvage and vision salvage with current treatment modalities. It requires integrated approach involving adequate screening, prompt referral and a team of ophthalmologist and pediatric oncologist at a comprehensive tertiary care centre.

- Our study shows that patients with retinoblastoma seek treatment at late stage of disease due to lack of awareness and delayed access to tertiary health care. This highlights the need for improved awareness among public and primary health care providers so that diagnosis can be made at an early stage.

PART 3

BIBLIOGRAPHY

[1] Lennox EL, Draper GJ, Sanders BM. Retinoblastoma: a study of natural history and prognosis of 268 cases. Br Med J 1975; 3:731–4.

[2] Arora RS, Eden T, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer. 2009; 46: 264-73.

[3] Matthew WW, Barrett GH, Carlos RG. Socioeconomic impact of modern multidisciplinary management of retinoblastoma. *Pediatrics* 2006; **118**: 331–336.

[4] Tambolli A, PodgorMJ, HormJW. The incidence of retinoblastoma in the United States: 1974 through 1985. Arch Ophthalmol 1990; 108: 128-32.

[5] Karcioglu ZA, al-Mesfer SA, Abboud E, Jabak MH, Mullaney PB.: Workup for metastatic retinoblastoma. A review of 261 patients. Ophthalmology. 1997 Feb; 104(2):307-12.

[6] Pawius P. Observatio XXIII. Tumor oculorum. In: Observationes Anatomicae Selectiores. Appended to: Bartholinus T. Historiarum Anatomicarum Rariorum, Centuria III & IV. Copenhagen, Denmark: Petrus Morsing; 1657:38-39.

[7] Hey W. Practical Observations in Surgery. Philadelphia, Pa: James Humphreys; 1805.

[8] Wardrop J. Observations on the fungus haematodes. Edinburgh: Constable; 1809.

[9] Virchow R. Die Drankhaften Geschwulste. Berlin, Germany: Harshwald; 1864.

[10] Flexner S. A peculiar glioma (neuroepithelioma) of the retina. Bull Johns Hopkins Hosp. 1891;2.

[11] Verhoeff FH, Jackson E. Minutes of the proceedings of the 62nd annual meeting. Trans Am Ophthalmol Soc. 1926;24:38-43.

[12] Albert DM. Historic review of retinoblastoma. Ophthalmology 1987; 94: 654–62.

[13] Young JL, Smith MA, Roffers SD, et al. Retinoblastoma. In: Cancer Incidence and Survival among Children and Adolescents: United States SEER Program, 1975-1995, Ries LA, Smith MA, Gurney JG, et al (Eds), National Cancer Institute, Bethesda, MD 1999. p.73.

[14] Devesa SS. The incidence of retinoblastoma. Am J Ophthalmol. 1975;80(2):263.

[15] Tamboli A, Podgor MJ, Horm JW. The incidence of retinoblastoma in the United States: 1974 through 1985. Arch Ophthalmol. 1990; 108(1):128.

[16] RubenfeldM, Abramson DH,Ellsworth RM, Kitchin FD. Unilateral vs. bilateral retinoblastoma: correlations between age at diagnosis and stage of ocular disease. Ophthalmology 1986; 93: 1016-9.

[17] Suckling RD, Fitzgerald PH, Stewart J et al. The Incidence and Epidemiology of Retinoblastoma in New Zealand: A 30-year survey. Br J Cancer. 1982; 46: 729.

[18] Sparkes RS, Murphree AL, Lingua RW, et al. Gene for hereditary retinoblastoma assigned to human chromosome 13 by linkage to esterase D. Science 1983; 219:971–3.

[19] Knudson Ag, Jr.: Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A 68:820-3, 1971.

[20] Hethcote HW, Knudson AG Jr. Model for the incidence of embryonal cancers: Application to retinoblastoma. Proc Natl Acad Sci U S A 1978; 75:2453-2457.

[21] Friend SH, Bernards R, Rogelj S, et al. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature 1986; 323: 643-646.

[22] Lohmann DR, Gallie BL. Retinoblastoma: Revisiting the model prototype of inherited cancer. Am J Med Genet C Semin Med Genet 2004; 129: 23-28.

[23] Bookstein R, Lee EY, To H, et al. Human retinoblastoma susceptibility gene: genomic organization and analysis of heterozygous intragenic deletion mutants. Proc Natl Acad Sci U S A. 1988; 85: 2210-22.

[24] Hong FD, Huang HJ, To H, et al. Structure of the human retinoblastoma gene. Proc Natl Acad Sci U S A. 1989; 86:5502-5506.

[25] Zhu XP, Dunn JM, Phillips RA, et al. Preferential germline mutation of the paternal allele in retinoblastoma. Nature 1989;340:312-313.

[26] Prevalence of high-risk human papillomavirus genotypes in retinoblastoma.Bhuvaneswari Anand, C Ramesh, L Appaji, B S Aruna Kumari, A M Shenoy, Nanjundappa, R S Jayshree, Rekha V Kumar. Br J Ophthalmol. 2011 Jul;95(7):1014-8.

[27] Kopelman JE, McLean IW. Multivariant analysis of clinical and histological risk factors for metastatic retinoblastoma. Invest Ophthalmol Vis Sci. 1983;24(suppl):50

[28] Gallie BL, Ellsworth RM, Abramson DH, et al. Retinoma: spontaneous regression of retinoblastoma or benign manifestation of the mutation? Br J Cancer. 1982;45:513-521.

[29] Intraocular tumours. An atlas and textbook. Shields JA, Shields CL.2nd edition. Chapter 17; 327-332.

[30] Margo C, Hidayat A, Kopelman J, et al. Retinocytoma: a benign variant of retinoblastoma. Arch Ophthalmol. 1983;101:1519-1531.

[31] Abramson DH, Frank CM, Susman M, Whalen MP, Dunkel IJ, Boyd NW et al. Presenting signs of Retinoblastoma. Pediatrics 1998 Mar; 132: 505-8.

[32] Balasubramanya R, Pushker N, Bajaj MS, Ghose S, Kashyap S, Rani A.: Atypical presentations of retinoblastoma. J Pediatr Ophthalmol Strabismus. 2004 Jan-Feb; 41(1):18-24.

[33] Demographics, clinical profile, management, and outcome of retinoblastoma in a tertiary care center in southern India. V. P. Reddy, S. G. Honavar, D. Shome, K. Shah, M. N. Naik and R. Rao. Journal of Clinical Oncology, 2007.Vol 25, No 18S.

[34] Sahu S, Banavali SD, Pai SK, Nair CN, Kurkure PA, Motwani SA, Advani SH. Retinoblastoma: problems and perspectives from India. Pediatr Hematol Oncol. 1998 Nov-Dec; 15(6):501-8.

[35] Dhir, S P.; Jain, I.S. and Das, S.K.Survival of retinoblastoma cases in North India. , 1977 Indian J. Ophthalmol. 24 :35, 1977.

[36] Zhao J, Li S, Shi J, Wang N. Clinical presentation and group classification of newly diagnosed intraocular retinoblastoma in China. Br J Ophthalmology. 2011 Oct; 95(10):1372-5.

[37] Donaldson S, Egbert P, Newsham I, et al: Retinoblastoma. In Principles and Practice of Pediatric Oncology (Pizzo P, Poplack D, eds).Philadelphia: Lippincoltt-Raven, 1997, pp 699.

[38] Shields CL, Shields JA. Basic under standing of current classification and management of retinoblastoma. Curr Opin Ophthalmol.2006;17: 228-34.

[39] Ellsworth RM. The practical management of retinoblastoma. Trans Am Ophthalmol Soc 1969: 67: 462-534.

[40] MacKay CJ, Abramson DH, Ellsworth RM. Metastatic patterns of retinoblastoma. Arch Ophthalmol 1984; 102:391–6.

[41] Shields CL, Shields JA. Recent developments in the management of retinoblastoma. J Pediatr Ophthalmol Strabismus 1999; 36: 8–18.

[42] Murthy R, Honavar SG, Naik MN, Reddy VA. Retinoblastoma. In: Dutta LC, ed. Modern Ophthalmology . New Delhi, India, Jaypee Brothers; 2004:849859.

[43] Stallard HB: The conservative treatment of retinoblastoma. Trans Am Op ththalmol Soc UK 1962; 82:473-534.

[44] Shields CL, Santos MC, Diniz W et al. Thermotherapy for retinoblastoma. Arch Ophthalmol 1999; 117: 885-893.

[45] Shields CL, Shields JA, Cater J et al. Plaque radiotherapy for retinoblas toma, long term tumor control and treatment complications in 208 tumors. Ophthalmology 2001;108: 2116-2121.

[46] Hungerford JL, Toma NMG, Plow man PN, Kingston JE. External beam ra diotherapy for retinoblastoma: I, wholeeye technique. Br J Ophthalmol. 1995; 79: 112-117.

[47] Ferris FL, 3rd, Chew EY. A new era for the treatment of retinoblastoma. Arch Ophthalmol 1996; 114:1412.

[48] Kingston JE, Hungerford JL, Madreperla SA, Plowman PN. Results of combined chemotherapy and radiotherapy for advanced intraocular retinoblastoma. Archives of Ophthalmology 1996; 114:1339-43.

[49] Shields CL, De Potter P, Himelstein BP, Shields JA, Meadows AT, Maris JM. Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol 1996; 114:1330-8.

[50] Intraocular tumours. An atlas and textbook. Shields JA, Shields CL.2nd edition. Chapter 18; 333-352.

[51] Abramson DH, Niksarli K, Ellsworth RM, Servodidio CA. Changing trends in the management of retinoblastoma: 1951-1965 vs 1966-1980. J Pediatr Ophthalmol Strabismus 1994.

[52] Honavar SG, Singh AD. Manage ment of advanced retinoblastoma. Ophthalmol Clin North Am. 2005;18:6573.

[53] Kopelman JE, McLean IW, Rosenberg SH. Multivariate analysis of risk factors for metastasis in retinoblastoma treated by enucleation. Ophthalmology 1987; 94:371-7.

[54] Messmer EP, Heinrich T, Hopping W, de Sutter E, Havers W, Sauerwein W. Risk factors for metastases in patients with retinoblastoma. Ophthalmology 1991; 98:136-41.

[55] Honavar SG, Singh AD, Shields CL, Demirci H, Smith AF, Shields JA. Postenucleation prophylactic chemotherapy in high- risk retinoblastoma. Arch Oph thalmol 2002; 120:923-31.

[56] Peylan-Ramu N, Bin Nun A, Skleir Levy M, et al. Orbital growth retardation in retinoblastoma survivors; work in progress. Med Pediatr Oncol 2001; 37(5): 465-70.

[57] K L Heher, J A Katowitz, J E Low. Unilateral dermis-fat graft implantation in the pediatric orbit. Ophthalmic Plastic and Reconstructive Surgery 1998) 14; 2: 81-88.

[58] Shanmugam MP, Biswas J, Gopal L, Sharma T, Nizamuddin SH. The clinical spectrum and treatment outcome of retinoblastoma in Indian children. J Pediatr Ophthalmol Strabismus. 2005; 42: 75-81.

[59] Azar, Donaldson, Craig. Retinoblastoma in New South Wales 1975 to 2001. Journal of Pediatric Hematology/Oncology: October 2006; 10: 642-646.

[60] Epidemiological characteristics of retinoblastoma in children attending the Mexican Social Security Institute in Mexico City, 1990-94. Pediatr Perinat Epidemiol; 16: 940: 370-4.

[61] Mukhopadhyay S, Ghosh S, Chattopadhyay D, Dutta SK. An observational study on retinoblastoma cases attending a medical college in Calcutta. J Indian Med Assoc. 2006; 104: 67-70.

[62] Retinoblastoma in Nepal: a clinical profile of 30 cases. Saiju R, Thakur J, Karmacharya PC, Shah DN. Nepal Med Coll J.2006 Sep; 8(3):171-5.

[63] V Essuman, C T Ntim-Amponsah, S Akafo, L Renner,and L Edusei. Presentation of Retinoblastoma at a Paediatric Eye Clinic in Ghana. Ghana Med J. 2010 March; 44(1): 10–15.

[64] Gupta R, Vemuganti GK, Reddy VA, Honavar SG. Histopathologic risk factors in retinoblastoma in India.Arch pathol lab med2009 Aug;133(8):1210-4.

[65] E Broaddus, A Topham, A D Singh. Survival with retinoblastoma in the USA: 1975–2004. Br J Ophthalmol 2009; 93:24-27 doi:10.1136/bjo.2.008.143842.

[66] Masood Naseripour, Khalil Ghasemi Falavarjani, Pejman Bakhtiari, Parvaneh Vosough, Farhad Aryan, MD4 Retinoblastoma Survival in Iran: 10 Years Experience of a Referral Center. Iranian Journal of Ophthalmology 2009;21(4):17-24.

[67] Arora RS, Eden TOB, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer.2010122;161: 71-72.

[68] American Academy of Pediatrics policy statement- Red Reflex Examination in Neonates, Infants, and Children. Pediatrics 2008;122(6) 1401-1404

PROFORMA

Name: Age: Sex: M/F

IP.NO: D.O.A:

Address:

Phone no:

Informant: mother/father/relative

First sign noticed:

1. Leucocoria
2. Squint
3. Red eye
4. Proptosis
5. Reduction in vision
6. Swelling of lids
7. Others

Other signs noticed:

Date of first sign:

Age at first sign:

Is there family history of retinoblastoma: yes/no

Is there family history of other cancers: yes/no

Examination:

General examination: nutrition pallor

Lymphnodes

Other swellings

Ocular examination:

Eye affected : right/left/both

	Right eye	left eye
Eyelids		
Conjunctiva		
sclera		
Cornea		

Anterior chamber

Iris

Pupil

Lens

Fundus

International Classification for Intraocular Disease

	Right eye	left eye
Group A		
Group B		
Group C		
Group D		
Group E		

Investigations: Hb: Peripheral smear:

BMA: B-Scan:

CT/MRI:

X-Ray chest:

CSF analysis:

Treatment:

Enucleation Primary chemotherapy

Primary chemotherapy+radiotherapy

Adjuvant chemotherapy/radiotherapy

Focal therapy

Description of treatment given:

HPE: choroidal invasion/ extrascleral invasion/ optic nerve infiltration

Classification of Retinoblastoma

Stage: 0 l ll llla/b lVa/b

Follow-up:

Ocular examination:

Investigation done:

Survival during study period: yes/no

Mortality:

Cause of death:

KEY TO MASTER CHART

M-male

F-female

RE- right eye

LE- left eye

P-proptosis

R-red eye

PH-pseudohypopyon

O-orbital cellulitis

Ch- choroid

CNS – central nervous system

PMMA- polymethyl methacrylate

EE- extraocular extension

I- iris invasion

CHE-chemotherapy

1-primary

2-secondary

L--leucocoria

E- enucleation

C-calcification

ON – optic nerve

R-radiotherapy

MASTER CHART

S.No	name	age(months)	sex	eye	presenting signs	time lag(weeks)	imaging	MRI	group	treatment	hpe	stage	implant	follow-up
1	hari	24	M	RE	L+R	24	C		E	E	Ch	I		no rec
2	sarathy	24	M	LE	L+R	13	NO C	CNS	E	E+CHR+R	EE+0N	IVb		died at 5years
3	karishma	1	F	RE	L	4	C		D					refused treatment
3	karishma	1	F	LE	R	4	C		E					refused treatment
4	pavithra	96	F	LE	L	3	C	ON	E	E+CHR	ON invasion	II		no rec
5	isak	30	M	RE	L	3	C		D	CHR+R+E	NO ON Iinvasion	I	1 PMMA	no rec
6	praveena	18	F	RE	R	1	C		E	E+CHR	Ch invasion	I		no rec
7	gayathri	48	F	RE	L	1	C		D	CHR		0		no rec
8	vijay	11	M	RE	L	2	C		D	E+CHR+R	no ON invasion	IVb		lost to follow
8	vijay	11	M	LE	exam	0	C	CNS	C	CHR+R		IVb		lost to follow
9	chandrasekar	3	M	LE	L	2	C		D	E	no ON invasion	I		no rec
10	siva	24	M	LE	L+P	8	C		E	E+CHR+R	Ch invasion	IVa		bony mets.died at 6 yrs
10	siva	24	M	LE	enucleated	1	C		D	E	no ON invasion	IVa		died at 6 years
11	dhanim ansari	36	M	LE	L	3	C		D	E+CHR	no ON invasion	I		no rec
12	sakthi	3	F	RE	L+R	8	C		D	E	no ON invasion	I	2 PMMA	no rec
12	sakthi	3	F	LE	L+R	8	C		E	E	no ON invasion	I	2 PMMA	no rec
13	priya	24	F	LE	L	2	C		D	E	no ON invasion	I		no rec
14	nithya priya	3	F	RE	L	2	C		D	CHR		0		died at 4 months
14	nithya priya	3	F	LE	L	2	C		D	CHR		0		died at 4 months
15	sumathy	36	F	RE	L	1	C		D	E	no ON invasion	I		no rec
16	ansh	30	M	LE	P	13	C	EE	E	CHE+R+E	ON+EE	IIIa		no rec
17	dhanalakshmi	12	F	LE	L	1	C		D	E	no ON invasion	I		no rec
18	surya	30	F	LE	L	5	C		D					refused treatment
18	surya	30	F	RE	L	5	C		D					refused treatment
19	pushpa	36	F	LE	O	10	C	ON	E	E+CHR	ON + Ch invasion	II		no rec
20	sindhya	60	F	LE	exam	0	C		C	CHR	Ch invasion	0		no rec
20	sindhya	60	F	RE	L	1	C		D	E	no ON invasion	I	1 PMMA	no rec
21	kaviya	24	F	RE	L	2	C		D	E	no ON invasion	I	2 dermis fat	no rec
22	avinash	3	M	LE	L	2	C		D	CHR		0		no rec
22	avinash	3	M	RE	L	2	C	ON	D	E+CHR		II		no rec
23	shanmugam	36	M	RE	PH	4	C		E	E+CHR	I	I	1 PMMA	no rec
24	ekavathi	36	F	LE	L	4	NO C		D	E	no ON invasion	I		no rec
25	goutham	60	M	RE	P	10	C	EE	E	E+CHR	EE+ON	II		died at 7 years
26	vinitha	36	F	LE	L	1	C		D	E	no ON invasion	I		no rec
27	jehangir	18	M	RE	L	2	C		D	E	no ON invasion	I		no rec
28	sagariya	48	M	RE	L	1	C		D	E+CHR+R	Ch	I	1 PMMA	no rec